Current Science
CS 4 (4), 625– 640 (2024)
Received 25 May 2024 | **Revised** 25 June 2024 | **Accepted** 25 July 2024 | **Online Available** 30 August 2024
https://doi.org/10.52845/CS/2024-4-4-5

Current Science

Current Science

OPEN ACCESS

ISSN (O) 2795-8639

ORIGINAL ARTICLE

Plasma Proteomic Biomarkers of Aplastic Anemia: A Study Based On Genome-Wide Association Studies Data

Angui Liu[1*], Xianwei Peng[1]*, Yiting Zhang[1], Yinghui Lai[1]

[1]Department of Hematology, The Second Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region 530000, P. R. China.

Corresponding Author: Professor Yinghui Lai

Abstract:
This study aims to explore the association between 4907 plasma proteins and genetic susceptibility to aplastic anemia (AA). Genetic associations with levels of 4907 plasma proteins were extracted from a large-scale protein quantitative trait loci study involving 35,559 Icelanders, with data sourced from deCODE GENETICS. Additionally, an aplastic anemia-related genome-wide association study (GWAS) dataset (ebi-a-GCST90018794) was obtained from the IEU OpenGWAS project, which conducted a GWAS on 473,500 European individuals analyzing approximately 24,192,378 SNPs following quality control and imputation. Inverse variance weighting and MR Egger methods, implemented via R packages, were primarily used to assess the causal associations between 4907 plasma proteins and aplastic anemia. The Mendelian randomization (MR) analysis revealed 12 types of plasma proteins associated with decreased genetic susceptibility to AA. The inverse variance weighting (IVW) results indicated significant associations for several proteins, including CCL25 (odds ratio (OR), 0.868; 95% confidence interval (CI), 0.790–0.954; p=0.003), DSG2 (OR, 0.882; 95% CI, 0.795–0.979; p=0.018), EPHA4 (OR, 0.896; 95% CI, 0.824–0.975; p=0.011), EPHB4 (OR, 0.876; 95% CI, 0.782–0.981; p=0.022), IL3RA (OR, 0.860; 95% CI, 0.788–0.938; p <0.001), MDGA2 (OR, 0.906; 95% CI, 0.832–0.986; p=0.022), MET (OR, 0.871; 95% CI, 0.777–0.976; p=0.017), PEAR1 (OR, 0.868; 95%CI, 0.766–0.985; p=0.028), PLXND1 (OR, 0.914; 95% CI, 0.849–0.985; p=0.018), SELE (OR, 0.889; 95% CI, 0.821–0.963; p=0.004), and TLL1 (OR, 0.844; 95% CI, 0.725–0.982; p =0.028), all showing a reduced genetic susceptibility to AA. Conversely, MMP7 was associated with an increased genetic susceptibility to AA (OR, 1.211; 95% CI, 1.011–1.452). The pathway analysis showed that 12 plasma proteins were enriched in Cytokine-cytokine receptor interaction and PI3K-Akt signaling pathway. In summary, our MR study systematically evaluated the causal relationships between plasma protein biomarkers and AA, identifying 12 plasma proteins that have a causal influence on AA.

Key Words: Aplastic anemia, Mendelian randomization, plasma protein, GWAS

Introduction

Aplastic anemia (AA) is a bone marrow failure syndrome characterized by diminished proliferation of bone marrow hematopoietic cells and pancytopenia. The primary clinical manifestations include anemia, bleeding, and infection. The pathogenesis of AA is intricately linked to external cytotoxic agents, mutations in DNA repair, telomere maintenance, or hematopoiesis-related genes, and immune-mediated damage to the bone marrow microenvironment[1]. Epidemiological studies indicate that the incidence of AA in China is approximately 0.7 cases per 100,000 people, which is 2-3 times higher than that observed in Western countries. In addition, the prevalence of AA in China is on the rise, contributing significantly to the socioeconomic burden on the nation, society, and individual patients[2].

Proteins are key regulatory elements in molecular pathways and have become primary targets in drug development. The plasma proteome,

comprising circulating proteins produced by cells and tissues, is secreted into the circulation during periods of cell damage or function[3]. In 2021, Ferkingstad E et al. reported GWAS data for 4907 plasma proteins from 35,559 Icelanders, establishing a foundational dataset for exploring the relationship between plasma proteins and human diseases[4]. Numerous studies have demonstrated a strong association between plasma proteins and the development of conditions such as deep vein thrombosis[3], stroke[5], complications of diabetes[6-7], multiple myeloma[8], cardiovascular diseases[9-10], and mental disorders[11], highlighting their potential as therapeutic targets. Therefore, a comprehensive analysis of the causal relationship between plasma proteins and aplastic anemia may shed light on the pathogenesis of AA and could also identify potential therapeutic targets for its treatment.

Mendelian randomization (MR) is an epidemiological method that enhances causal inference by using genetic variants as instrumental variables for exposure factors, such as plasma proteins[3]. MR is considered a natural random experiment, which assesses the potential causal relationships between exposure factors, such as plasma proteins, and diseases, such as aplastic anemia. This method involves the random allocation of individuals to subgroups at conception based on genetic variants, during which confounding factors are also randomized [5]. In our study, we used protein and genetic data reported by Ferkingstad E et al. in the Icelandic population to conduct cohort and MR analyses to explore the relationship between 4907 plasma proteins and the risk of AA.

Materials and Methods

Study Design

The study design is illustrated in Figure 1. We used MR to investigate the causal relationship between 4907 circulating proteins and AA, relying on publicly available data from a large-scale genome-wide association study of the blood proteome. The data were obtained from deCODE GENETICS (https://www.decode.com/ summary data/)(4) and the IEU OpenGWAS project(12).

Figure 1. The main design of this study. (A)The data sources and processing of this study. (B)Assumptions of the Mendelian randomization analysis for plasma proteins and aplastic anemia.

4907 circulating proteins and related GWAS data sources

Genetic associations with levels of 4907 plasma proteins were derived from a large-scale protein quantitative trait loci (pQTL) study involving 35,559 Icelanders, with data sourced from deCODE GENETICS. At deCODE GENETICS, raw pQTL data on plasma proteins are accessible by providing information such as name, email address, and organization. Our processing of the raw data included several key steps: initially, correlation analysis was conducted using the TwoSampleMR package. The current study focused on proteins with pQTLs identified at the genome-wide significance level ($P < 5 \times 10^{-8}$) in two-sample MR analyses. Secondly, to address linkage disequilibrium, SNPs were filtered based on criteria including an $r^2 = 0.001$ and kb = 10000. Thirdly, weak instrumental variables were excluded, retaining only those with an F-statistic greater than 10.

Outcome data sources

An AA-related GWAS dataset (ebi-a-GCST90018794) was sourced from the IEU

OpenGWAS project(12). This dataset conducted a GWAS on 473,500 European individuals, analyzing approximately 24,192,378 SNPs following quality control and imputation. For the analysis, data was directly extracted using R packages, with a significance threshold of $P < 1\times10^{-8}$ for inclusion in the correlation analysis. The criteria for removing linkage disequilibrium SNPs and weak instrumental variables were consistent with those used in the processing of protein data.

Enrichment analysis

The GO enrichment analysis including molecular function (MF), cellular components (CC) and biological processes (BP). ClusterProfiler package was used to performed GO and KEGG pathway analysis.

Statistical analysis

R 4.4 software (http://www.Rproject.org) was utilized to performed MR analysis. To access the causal association between 4907 plasma proteins and AA, inverse variance weighting (IVW)(13) and MR Egger methods were primarily used via the 'TwoSampleMR' package (version 0.6.3), 'VariantAnnotation' package, and 'gwasglue' package. Cochran's Q was used to access heterogeneity, and a p-value ≥ 0.05 indicated a lack of heterogeneity in the results. Additionally, leave-one-out methods were utilized to conduct a sensitivity analysis.

Results

Two-sample MR analysis

SNPs related to 4907 plasma proteins were identified after correlation analysis, removal of linkage disequilibrium, and exclusion of weak instrumental variables. AA-related SNPs were calculated based on the ebi-a-GCST90018794 dataset. In our study, we intersected the results obtained from IVW and MR Egger methods. The MR analysis identified 12 types of plasma proteins associated with decreased genetic susceptibility to AA. SNPs related to 12 plasma proteins were illustrated in **Supplementary Table 1**. The IVW results indicated that CCL25 (odds ratio (OR), 0.868; 95% confidence interval (CI), 0.790–0.954; p=0.003), DSG2 (OR, 0.882; 95% CI, 0.795–0.979; p=0.018), EPHA4 (OR, 0.896; 95% CI, 0.824–0.975; p=0.011), EPHB4 (OR, 0.876; 95% CI, 0.782–0.981; p=0.022), IGF1R (OR, 0.855; 95% CI, 0.736–0.994; p=0.041), IL3RA (OR, 0.860; 95% CI, 0.788–0.938; p <0.001), MDGA2 (OR, 0.906; 95% CI, 0.832–0.986; p=0.022), MET (OR, 0.871; 95% CI, 0.777–0.976; p=0.017),PEAR1 (OR, 0.868; 95% CI, 0.766–0.985; p=0.028), PLXND1 (OR, 0.914; 95% CI, 0.849–0.985; p=0.018), SELE (OR, 0.889; 95% CI, 0.821–0.963; p=0.004), and TLL1 (OR, 0.844; 95% CI, 0.725–0.982; p=0.028) were associated with decreased genetic susceptibility to AA. Conversely, MMP7 was associated with an increased genetic susceptibility to AA with an OR of 1.211 (95% CI, 1.011–1.452). The visualizations are depicted in Figures 2, 3, and 4. MR-Egger analysis indicates that only IGF1R exhibits horizontal pleiotropy (Table 1**)**.

Supplementary Table 1.1 Information of identified SNPs in exposure (CCL25) and outcomes (AA).

				Exposure (CCL25)			Outcome (AA)				
	SNP	**EA**	**OA**	**β**	**SE**	***p* value**	**Case**	**Control**	**β**	**SE**	***p* value**
1	rs12279699	A	G	0.0957	0.012215	4.71E-15	4,128	469,372	0.0122	0.0329	0.7121
2	rs12718462	C	T	0.0985	0.015271	1.12E-10	4,128	469,372	-0.0064	0.043	0.8809
3	rs12980552	G	A	-0.2686	0.00845	1.00E-200	4,128	469,372	0.0689	0.0224	0.00210601
4	rs12983058	T	G	-0.0583	0.009491	8.11E-10	4,128	469,372	0.0093	0.026	0.721
5	rs1501908	C	G	0.0945	0.008452	5.06E-29	4,128	469,372	0.0091	0.0238	0.702499
6	rs16854775	G	C	-0.0526	0.009468	2.77E-08	4,128	469,372	-0.0128	0.0257	0.6183
7	rs17438280	C	G	0.1345	0.016761	1.02E-15	4,128	469,372	-0.0695	0.0628	0.2688
8	rs181528492	C	T	-0.531	0.039901	2.08E-40	4,128	469,372	-0.0512	0.1243	0.680299

9	rs214068	C	T	-0.1469	0.008267	1.23E-70	4,128	469,372	0.0361	0.0226	0.111
10	rs4804273	A	G	-0.1678	0.011099	1.23E-51	4,128	469,372	0.0016	0.0278	0.9539
11	rs4841427	G	A	0.1036	0.014533	1.01E-12	4,128	469,372	0.0694	0.04	0.0824992
12	rs59141216	C	T	-0.2861	0.026131	6.74E-28	4,128	469,372	-0.0208	0.0461	0.6521
13	rs601338	A	G	-0.1706	0.008761	1.89E-84	4,128	469,372	0.0193	0.0232	0.4054
14	rs62126622	G	T	-0.2516	0.025177	1.63E-23	4,128	469,372	0.1611	0.118	0.1722
15	rs635634	C	T	0.1208	0.012098	1.76E-23	4,128	469,372	-0.0733	0.028	0.00896107
16	rs72654473	A	C	0.0952	0.015118	3.03E-10	4,128	469,372	0.0308	0.0416	0.4584
17	rs78039161	C	T	-0.3085	0.01346	2.99E-116	4,128	469,372	0.0444	0.0335	0.1842
18	rs80188016	T	C	-0.1929	0.024195	1.55E-15	4,128	469,372	0.0853	0.1152	0.4589

SNP, single nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; AA, aplastic anemia.

Supplementary Table 1.2 Information of identified SNPs in exposure (DSG2) and outcomes (AA).

				Exposure (DSG2)			**Outcome (AA)**				
	SNP	**EA**	**OA**	**β**	**SE**	**p value**	**Case**	**Control**	**β**	**SE**	**p value**
1	rs1020839	T	C	-0.0893	0.011092	8.20E-16	4,128	469,372	0.016	0.0349	0.6455
2	rs10901252	C	G	0.4375	0.016569	1.20E-153	4,128	469,372	-0.0915	0.034	0.00709104
3	rs11078597	C	T	-0.0548	0.009896	3.06E-08	4,128	469,372	0.0204	0.0286	0.4754
4	rs117225497	T	G	-0.2146	0.036255	3.24E-09	4,128	469,372	0.1279	0.2975	0.6672
5	rs1231281	A	G	-0.0473	0.00825	9.85E-09	4,128	469,372	0.0166	0.0228	0.4681
6	rs147145691	T	C	-0.2669	0.028244	3.40E-21	4,128	469,372	0.0035	0.0731	0.9616
7	rs148666188	C	T	-0.298	0.038987	2.11E-14	4,128	469,372	0.1304	0.1095	0.2337
8	rs149181677	T	C	0.1572	0.021326	1.69E-13	4,128	469,372	0.0389	0.0472	0.4104
9	rs150816167	C	T	0.1402	0.019401	4.96E-13	4,128	469,372	-0.0544	0.0479	0.2559
10	rs537879	G	T	-0.1208	0.008187	2.85E-49	4,128	469,372	-0.0241	0.0225	0.2842
11	rs62578578	A	G	0.1761	0.023065	2.26E-14	4,128	469,372	0.0686	0.1065	0.5196
12	rs6905288	A	G	-0.0608	0.008237	1.57E-13	4,128	469,372	-6.00E-04	0.0227	0.9797
13	rs708686	T	C	0.0869	0.009689	3.01E-19	4,128	469,372	0.0216	0.024	0.367
14	rs75426668	A	G	-0.1675	0.025716	7.35E-11	4,128	469,372	-0.0058	0.0945	0.9508
15	rs9286383	T	A	-0.1041	0.014204	2.32E-13	4,128	469,372	0.0105	0.0357	0.768799
16	rs9304098	T	G	-0.1905	0.008195	1.58E-119	4,128	469,372	0.0295	0.0227	0.1942

SNP, single nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; AA, aplastic anemia.

Supplementary Table 1.3 Information of identified SNPs in exposure (EPHA4) and outcomes (AA).

				Exposure (EPHA4)			**Outcome (AA)**				
	SNP	**EA**	**OA**	**β**	**SE**	**p value**	**Case**	**Control**	**β**	**SE**	**p value**
1	rs112155714	G	A	-0.3285	0.03962	1.12E-16	4128	469372	-0.0146	0.0907	0.8724
2	rs114022440	G	A	0.2539	0.029843	1.77E-17	4128	469372	-0.0208	0.0653	0.7503

3	rs118167234	C	A	-0.2116	0.028364	8.644E-14	4128	469372	-0.0229	0.0678	0.735201
4	rs1260326	C	T	0.0577	0.008624	2.217E-11	4128	469372	0.0027	0.0234	0.9087
5	rs13108218	G	A	0.0486	0.008403	7.296E-09	4128	469372	-0.034	0.0239	0.1558
6	rs190696118	C	A	-0.2114	0.030226	2.671E-12	4128	469372	0.0669	0.1209	0.5798
7	rs28477937	T	C	-0.0575	0.00899	1.597E-10	4128	469372	-0.0073	0.0244	0.7635
8	rs4661359	T	C	-0.0677	0.008334	4.527E-16	4128	469372	-0.0007	0.0247	0.9771
9	rs4674589	C	T	0.0882	0.008224	7.765E-27	4128	469372	0.0145	0.0225	0.5182
10	rs62572818	G	C	0.1177	0.014448	3.747E-16	4128	469372	-0.016	0.055	0.771401
11	rs62576557	G	A	-0.1326	0.024311	4.916E-08	4128	469372	0.1241	0.0704	0.0777607
12	rs72704449	C	T	0.1361	0.019297	1.75E-12	4128	469372	-0.0512	0.0476	0.2825
13	rs739468	G	T	0.4201	0.013885	1E-200	4128	469372	-0.0659	0.0318	0.0385496
14	rs7470777	G	A	0.5414	0.017662	1E-200	4128	469372	-0.0532	0.0344	0.1215
15	rs75212266	A	G	-0.3341	0.039348	2.051E-17	4128	469372	0.0882	0.0886	0.3193
16	rs77924615	A	G	-0.0605	0.010252	3.603E-09	4128	469372	-0.0439	0.0272	0.1067

SNP, single nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; AA, aplastic anemia.

Supplementary Table 1.4 Information of identified SNPs in exposure (EPHB4) and outcomes (AA).

				Exposure (EPHB4)			Outcome (AA)				
	SNP	**EA**	**OA**	**β**	**SE**	**p value**	**Case**	**Control**	**β**	**SE**	**p value**
1	rs1260326	C	T	0.0475	0.008637	3.801E-08	4128	469372	0.0027	0.0234	0.9087
2	rs13108218	G	A	0.0511	0.008471	1.614E-09	4128	469372	-0.034	0.0239	0.1558
3	rs143616286	C	G	0.0972	0.017753	4.375E-08	4128	469372	0.0207	0.0421	0.6236
4	rs314366	A	G	0.1105	0.008151	7.183E-42	4128	469372	0.0268	0.0226	0.2368
5	rs35061193	T	C	-0.0531	0.008188	8.864E-11	4128	469372	-0.0892	0.0624	0.1528
6	rs41307428	T	C	0.3503	0.029219	4.062E-33	4128	469372	-0.0609	0.037	0.1004
7	rs635634	C	T	0.3847	0.012067	1E-200	4128	469372	-0.0733	0.028	0.00896107
8	rs724444	T	C	-0.0662	0.0101	5.575E-11	4128	469372	0.0037	0.025	0.8833
9	rs72704449	C	T	0.1328	0.019413	7.884E-12	4128	469372	-0.0512	0.0476	0.2825
10	rs7329478	G	A	-0.0703	0.011739	2.115E-09	4128	469372	0.0123	0.0284	0.6648
11	rs77924615	A	G	-0.0634	0.010329	8.367E-10	4128	469372	-0.0439	0.0272	0.1067
12	rs9558661	T	C	-0.0902	0.009721	1.719E-20	4128	469372	0.0001	0.028	0.9959

SNP, single nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; AA, aplastic anemia.

Supplementary Table 1.5 Information of identified SNPs in exposure (IL3RA) and outcomes (AA).

				Exposure (IL3RA)			Outcome (AA)				
	SNP	**EA**	**OA**	**β**	**SE**	**p value**	**Case**	**Control**	**β**	**SE**	**p value**
1	rs10850034	A	T	0.0459	0.008362	4.04E-08	4128	469372	0.0478	0.0693	0.4905
2	rs11066301	G	A	0.0457	0.008345	4.343E-08	4128	469372	-0.0094	0.023	0.682801
3	rs112564808	C	T	0.1636	0.028861	1.44E-08	4128	469372	-0.1128	0.0673	0.0935901
4	rs11507716	T	C	-0.2689	0.01329	4.929E-91	4128	469372	0.0822	0.0355	0.0204099
5	rs115676813	T	C	0.2368	0.038672	9.164E-10	4128	469372	0.0551	0.067	0.411
6	rs11603123	A	G	0.2399	0.020536	1.572E-31	4128	469372	-0.0529	0.0619	0.3923
7	rs117241334	A	C	0.3244	0.029933	2.283E-27	4128	469372	0.0961	0.0966	0.3198
8	rs117369137	A	G	-0.3111	0.038077	3.079E-16	4128	469372	0.075	0.1245	0.546799
9	rs117877056	A	C	0.2605	0.026803	2.499E-22	4128	469372	0.1677	0.1096	0.1259

10	rs2622935	G	A	-0.124	0.009454	2.673E-39	4128	469372	-0.0142	0.0256	0.578801
11	rs28367690	G	A	-0.0624	0.009738	1.478E-10	4128	469372	-0.0332	0.0699	0.635
12	rs2940174	A	T	-0.0995	0.016327	1.1E-09	4128	469372	0.0253	0.0647	0.695799
13	rs34250484	A	G	0.1943	0.016553	8.107E-32	4128	469372	0.0324	0.0447	0.4685
14	rs35434910	A	T	-0.3434	0.010962	1E-200	4128	469372	0.0771	0.0274	0.00499298
15	rs3793628	C	T	0.085	0.009266	4.599E-20	4128	469372	-0.0107	0.027	0.691899
16	rs4802117	A	G	0.0737	0.008041	4.916E-20	4128	469372	0.021	0.0233	0.3683
17	rs517076	A	G	0.0675	0.010858	5.089E-10	4128	469372	-0.039	0.0308	0.2056
18	rs61764072	C	A	0.3043	0.036335	5.526E-17	4128	469372	-0.0112	0.1748	0.9488
19	rs9411492	T	C	-0.3289	0.009357	1E-200	4128	469372	0.0612	0.0239	0.01044
20	rs9842051	C	G	0.0546	0.009544	1.058E-08	4128	469372	0.017	0.0288	0.5553

SNP, single nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; AA, aplastic anemia.

Supplementary Table 1.6 Information of identified SNPs in exposure (MDGA2) and outcomes (AA).

				Exposure (MDGA2)			Outcome (AA)				
	SNP	**EA**	**OA**	**β**	**SE**	**p value**	**Case**	**Control**	**β**	**SE**	**p value**
1	rs10149770	A	G	0.0876	0.014043	4.438E-10	4128	469372	-0.0125	0.0362	0.730299
2	rs111629268	T	C	-0.1235	0.013036	2.695E-21	4128	469372	0.6078	0.5614	0.279
3	rs112351914	A	G	0.1872	0.020382	4.132E-20	4128	469372	-0.0222	0.0631	0.7248
4	rs116174082	A	G	1.0801	0.020399	1E-200	4128	469372	-0.1932	0.0911	0.0338197
5	rs12147146	C	T	0.596	0.033776	1.1E-69	4128	469372	-0.0536	0.0741	0.4695
6	rs139953520	G	A	0.5455	0.031984	3.173E-65	4128	469372	-0.0373	0.118	0.7519
7	rs146048337	T	C	0.1582	0.027517	8.965E-09	4128	469372	0.0279	0.1362	0.8378
8	rs147722382	T	C	-0.2174	0.039342	3.279E-08	4128	469372	-0.1305	0.3102	0.673899
9	rs148244051	T	G	0.1506	0.023549	1.603E-10	4128	469372	-0.0377	0.0729	0.604999
10	rs149817759	A	G	-0.369	0.033482	3.037E-28	4128	469372	0.1123	0.1104	0.3091
11	rs191390916	T	C	0.0614	0.008388	2.483E-13	4128	469372	0.0206	0.0682	0.7623
12	rs34231016	T	C	0.0616	0.011211	3.919E-08	4128	469372	0.0189	0.0392	0.630199
13	rs34489253	G	A	0.0874	0.008128	5.766E-27	4128	469372	-0.0282	0.0224	0.2088
14	rs4665972	C	T	0.0485	0.00816	2.787E-09	4128	469372	0.0207	0.0231	0.3713
15	rs4788706	G	A	-0.0425	0.007758	4.298E-08	4128	469372	0.0181	0.0224	0.4198
16	rs4900811	T	C	-0.5405	0.009024	1E-200	4128	469372	0.0467	0.0396	0.2392
17	rs57844210	G	A	-0.1191	0.016173	1.785E-13	4128	469372	0.0149	0.0409	0.7157
18	rs62621812	A	G	0.1446	0.024288	2.622E-09	4128	469372	-0.0811	0.0585	0.1657
19	rs75694823	C	A	0.3634	0.030385	5.767E-33	4128	469372	0.3048	0.2026	0.1325
20	rs77544995	C	T	-0.2403	0.022097	1.523E-27	4128	469372	0.0183	0.0652	0.7792
21	rs79827742	A	G	0.2189	0.022201	6.201E-23	4128	469372	0.0241	0.0558	0.6656
22	rs8011466	G	C	-0.1676	0.01896	9.606E-19	4128	469372	-0.039	0.0514	0.4487
23	rs849133	T	C	-0.043	0.00773	2.657E-08	4128	469372	-0.0463	0.0224	0.0390796

SNP, single nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; AA, aplastic anemia.

Supplementary Table 1.7 Information of identified SNPs in exposure (MET) and outcomes (AA).

				Exposure (MET)			Outcome (AA)				
	SNP	**EA**	**OA**	**β**	**SE**	**p value**	**Case**	**Control**	**β**	**SE**	**p value**
1	rs1041316	A	G	0.0729	0.009626	3.638E-14	4128	469372	-0.0361	0.0252	0.1517
2	rs10435378	A	G	0.1309	0.008365	3.41E-55	4128	469372	0.0141	0.0228	0.5354
3	rs11045856	G	T	0.0796	0.009942	1.18E-15	4128	469372	0.0223	0.0293	0.4462
4	rs11603123	A	G	0.1839	0.021361	7.353E-18	4128	469372	-0.0529	0.0619	0.3923

5	rs117210485	A	G	0.1952	0.029983	7.492E-11	4128	469372	-0.0343	0.038	0.3664
6	rs13226546	C	A	0.0715	0.008308	7.531E-18	4128	469372	-0.0244	0.0227	0.2831
7	rs138121767	T	C	0.1538	0.02152	8.874E-13	4128	469372	-0.0082	0.1002	0.9346
8	rs139974673	C	T	-0.1547	0.02534	1.028E-09	4128	469372	-0.0967	0.1296	0.4555
9	rs143779007	C	T	-0.153	0.024898	7.991E-10	4128	469372	0.224	0.153	0.1434
10	rs145179853	T	C	-0.2067	0.035196	4.283E-09	4128	469372	-0.0227	0.1189	0.8487
11	rs1604038	T	C	-0.0685	0.009461	4.49E-13	4128	469372	-0.062	0.0253	0.0142298
12	rs174562	G	A	0.0588	0.008518	5.1E-12	4128	469372	0.0022	0.0228	0.9244
13	rs2343551	C	A	0.0875	0.010993	1.725E-15	4128	469372	0.02	0.0271	0.4598
14	rs3827211	G	A	-0.0664	0.008414	2.981E-15	4128	469372	0.031	0.0228	0.1743
15	rs55714927	T	C	0.0573	0.010236	2.171E-08	4128	469372	-0.0274	0.0262	0.2964
16	rs635634	C	T	0.395	0.012281	1E-200	4128	469372	-0.0733	0.028	0.00896107
17	rs72784938	C	A	0.1215	0.014032	4.777E-18	4128	469372	-0.0538	0.0487	0.2693
18	rs77542162	G	A	0.3272	0.026162	6.848E-36	4128	469372	-0.109	0.1199	0.3631

SNP, single nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; AA, aplastic anemia.

Supplementary Table 1.8 Information of identified SNPs in exposure (PEAR1) and outcomes (AA).

				Exposure (PEAR1)			Outcome (AA)				
	SNP	**EA**	**OA**	**β**	**SE**	**p value**	**Case**	**Control**	**β**	**SE**	**p value**
1	rs114346493	T	C	0.1898	0.028966	5.66E-11	4128	469372	0.0993	0.1246	0.4255
2	rs12005199	A	G	0.0614	0.008704	1.733E-12	4128	469372	0.0177	0.0233	0.4476
3	rs12795076	C	T	0.1103	0.014435	2.157E-14	4128	469372	-0.114	0.1015	0.2612
4	rs1354034	C	T	-0.0664	0.008483	4.99E-15	4128	469372	-0.0048	0.0243	0.8448
5	rs140477301	C	T	0.1569	0.024472	1.442E-10	4128	469372	-0.0361	0.0632	0.5679
6	rs1555405	A	G	-0.0572	0.008986	1.944E-10	4128	469372	-0.0096	0.0237	0.6853
7	rs17490626	C	G	0.0782	0.011512	1.097E-11	4128	469372	-0.0345	0.036	0.3376
8	rs2230283	T	C	0.0595	0.008881	2.085E-11	4128	469372	-0.0033	0.0236	0.8894
9	rs2413593	G	A	0.0513	0.008397	9.984E-10	4128	469372	0.0289	0.0624	0.642899
10	rs3124761	C	T	0.1442	0.014145	2.098E-24	4128	469372	-0.0694	0.0321	0.03071
11	rs41556717	T	C	0.1597	0.028838	3.062E-08	4128	469372	0.0268	0.1087	0.8055
12	rs4661012	G	T	-0.191	0.008551	1.679E-110	4128	469372	0.0233	0.0231	0.3131
13	rs56115403	A	G	0.0643	0.010069	1.7E-10	4128	469372	-0.0343	0.0257	0.1818
14	rs60843925	C	T	-0.0892	0.013267	1.777E-11	4128	469372	0.0093	0.0294	0.7516
15	rs62578578	A	G	0.1542	0.02325	3.306E-11	4128	469372	0.0686	0.1065	0.5196
16	rs75179845	C	T	0.4601	0.016703	4.848E-167	4128	469372	-0.0863	0.0338	0.0105801
17	rs7776054	G	A	0.0566	0.009256	9.662E-10	4128	469372	0.0775	0.0239	0.00117999

SNP, single nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; AA, aplastic anemia.

Supplementary Table 1.9 Information of identified SNPs in exposure (PLXND1) and outcomes (AA).

				Exposure (PLXND1)			Outcome (AA)				
	SNP	**EA**	**OA**	**β**	**SE**	**p value**	**Case**	**Control**	**β**	**SE**	**p value**
1	rs111903631	C	T	0.1862	0.029615	3.228E-10	4128	469372	0.1708	0.1139	0.1337
2	rs11244084	T	C	-0.6117	0.017633	1E-200	4128	469372	0.0979	0.0504	0.0522396
3	rs11603123	A	G	0.2117	0.020758	2.018E-24	4128	469372	-0.0529	0.0619	0.3923
4	rs117241334	A	C	0.2303	0.030288	2.881E-14	4128	469372	0.0961	0.0966	0.3198

5	rs117369137	A	G	-0.2711	0.037646	5.962E-13	4128	469372	0.075	0.1245	0.546799
6	rs117633773	A	G	0.1177	0.019961	3.715E-09	4128	469372	-0.0004	0.0727	0.9954
7	rs117877056	A	C	0.1894	0.027122	2.882E-12	4128	469372	0.1677	0.1096	0.1259
8	rs12378537	T	C	0.5271	0.015814	1E-200	4128	469372	-0.0358	0.0326	0.2724
9	rs143501783	C	T	0.2995	0.036803	4.019E-16	4128	469372	-0.0334	0.1925	0.8621
10	rs150730585	A	G	-0.3136	0.032302	2.775E-22	4128	469372	-0.1224	0.1451	0.3992
11	rs2073926	T	A	0.1491	0.016735	5.137E-19	4128	469372	0.0437	0.0335	0.1919
12	rs2255703	C	T	-0.2129	0.008289	1.746E-145	4128	469372	0.0346	0.0237	0.1447
13	rs2477642	C	T	0.0479	0.008158	4.322E-09	4128	469372	0.0261	0.0245	0.2867
14	rs2837988	A	C	0.0554	0.008128	9.348E-12	4128	469372	-0.0129	0.0239	0.5887
15	rs28850104	T	C	-0.0954	0.008794	2.037E-27	4128	469372	0.0176	0.0248	0.478
16	rs2936613	T	G	-0.0664	0.010956	1.356E-09	4128	469372	0.0451	0.0268	0.0921595
17	rs3094377	C	T	0.5015	0.025814	4.507E-84	4128	469372	-0.0867	0.0609	0.1544
18	rs3135387	G	T	-0.0721	0.008737	1.556E-16	4128	469372	-0.0121	0.0274	0.658701
19	rs4857414	T	C	-0.0732	0.008224	5.521E-19	4128	469372	-0.0032	0.0225	0.8862
20	rs55714927	T	C	0.1186	0.009962	1.118E-32	4128	469372	-0.0274	0.0262	0.2964
21	rs62259780	G	T	0.0511	0.00896	1.176E-08	4128	469372	-0.0348	0.0257	0.175
22	rs62266917	T	C	-0.1374	0.014016	1.09E-22	4128	469372	0.0062	0.031	0.8421
23	rs62572818	G	C	0.1708	0.014745	4.989E-31	4128	469372	-0.016	0.055	0.771401
24	rs75876642	T	C	0.1712	0.025561	2.118E-11	4128	469372	-0.002	0.0579	0.9725
25	rs78705678	G	A	0.05	0.008409	2.745E-09	4128	469372	0.0531	0.0251	0.0343803

SNP, single nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; AA, aplastic anemia.

Supplementary Table 1.10 Information of identified SNPs in exposure (SELE) and outcomes (AA).

				Exposure (SELE)			Outcome (AA)				
	SNP	**EA**	**OA**	**β**	**SE**	**p value**	**Case**	**Control**	**β**	**SE**	**p value**
1	rs117603193	G	A	-0.3559	0.032154	1.783E-28	4128	469372	0.096	0.061	0.1153
2	rs141668780	C	T	-0.317	0.023951	5.496E-40	4128	469372	0.036	0.1023	0.725
3	rs1585488	T	G	-0.0738	0.008054	5.04E-20	4128	469372	-0.0055	0.0224	0.8072
4	rs2244608	G	A	0.0618	0.008718	1.353E-12	4128	469372	-0.0072	0.0233	0.756599
5	rs2519992	C	T	0.0632	0.008937	1.527E-12	4128	469372	-0.0912	0.0648	0.1592
6	rs28699275	T	C	0.21	0.021581	2.226E-22	4128	469372	-0.0249	0.0502	0.6204
7	rs35166255	A	G	0.3196	0.020762	1.812E-53	4128	469372	-0.0505	0.062	0.4147
8	rs3760775	T	G	0.1906	0.016553	1.117E-30	4128	469372	0.041	0.0371	0.2687
9	rs3917390	C	G	-0.1154	0.008604	5.078E-41	4128	469372	-0.0017	0.0238	0.9418
10	rs4545169	G	T	-0.0845	0.014279	3.265E-09	4128	469372	0.0027	0.0358	0.9402
11	rs55710199	T	C	-0.6218	0.031244	3.938E-88	4128	469372	0.1125	0.1291	0.3836
12	rs62061425	G	A	0.0677	0.009867	6.811E-12	4128	469372	-0.0346	0.0256	0.1762
13	rs62576476	T	C	-0.1858	0.023197	1.149E-15	4128	469372	0.0151	0.0539	0.779301
14	rs646776	T	C	0.1303	0.009993	7.308E-39	4128	469372	0.043	0.0273	0.1149
15	rs75212266	A	G	-0.5422	0.041276	2.049E-39	4128	469372	0.0882	0.0886	0.3193
16	rs7857390	G	A	-0.2846	0.008661	1E-200	4128	469372	0.0212	0.0232	0.36
17	rs7868232	C	T	-0.3511	0.010792	1E-200	4128	469372	0.0762	0.026	0.00331597

SNP, single nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; AA, aplastic anemia.

Supplementary Table 1.11 Information of identified SNPs in exposure (TLL1) and outcomes (AA).

			Exposure (TLL1)			Outcome (AA)				
SNP	**EA**	**OA**	**β**	**SE**	**p value**	**Case**	**Control**	**β**	**SE**	**p value**

1	rs13088856	G	T	0.0538	0.009063	2.916E-09	4128	469372	-0.015	0.0262	0.5657
2	rs1805482	A	G	-0.0481	0.008612	2.331E-08	4128	469372	-0.0232	0.0276	0.4018
3	rs1903176	A	T	-0.0586	0.008644	1.205E-11	4128	469372	-0.0019	0.0239	0.938
4	rs3815916	G	T	-0.0512	0.008421	1.202E-09	4128	469372	-0.0109	0.0226	0.630001
5	rs601338	A	G	-0.0932	0.008516	7.106E-28	4128	469372	0.0193	0.0232	0.4054
6	rs653178	T	C	0.0487	0.008552	1.237E-08	4128	469372	0.0064	0.0228	0.778901
7	rs66782572	G	A	-0.0568	0.008383	1.241E-11	4128	469372	0.066	0.0618	0.2854
8	rs739468	G	T	0.1184	0.014118	5.017E-17	4128	469372	-0.0659	0.0318	0.0385496
9	rs78705678	G	A	0.0588	0.00865	1.063E-11	4128	469372	0.0531	0.0251	0.0343803
10	rs8176743	T	C	0.4361	0.01686	1.627E-147	4128	469372	-0.0874	0.0337	0.00954289

SNP, single nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; AA, aplastic anemia.

Supplementary Table 1.12 Information of identified SNPs in exposure (MMP7) and outcomes (AA).

				Exposure (MMP7)			Outcome (AA)				
	SNP	**EA**	**OA**	**β**	**SE**	**p value**	**Case**	**Control**	**β**	**SE**	**p value**
1	rs12986064	C	T	-0.0661	0.008702	3.048E-14	4128	469372	0.0253	0.0228	0.2664
2	rs56857975	T	C	0.5671	0.016814	1E-200	4128	469372	0.1609	0.1292	0.2128
3	rs595151	C	A	-0.0502	0.008423	2.519E-09	4128	469372	0.0154	0.0226	0.4962
4	rs61729512	A	G	0.0787	0.01265	4.93E-10	4128	469372	0.0226	0.0322	0.4829
5	rs6694034	C	A	0.0848	0.008307	1.814E-24	4128	469372	0.0061	0.0226	0.786901
6	rs67702963	C	T	-0.1433	0.010239	1.668E-44	4128	469372	-0.0374	0.0263	0.1544
7	rs71480491	C	A	0.2669	0.027339	1.631E-22	4128	469372	0.0666	0.0622	0.2839
8	rs72981067	A	G	0.1992	0.034954	1.206E-08	4128	469372	0.0587	0.1712	0.731601
9	rs77924615	A	G	-0.1057	0.010532	1.063E-23	4128	469372	-0.0439	0.0272	0.1067

SNP, single nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; AA, aplastic anemia.

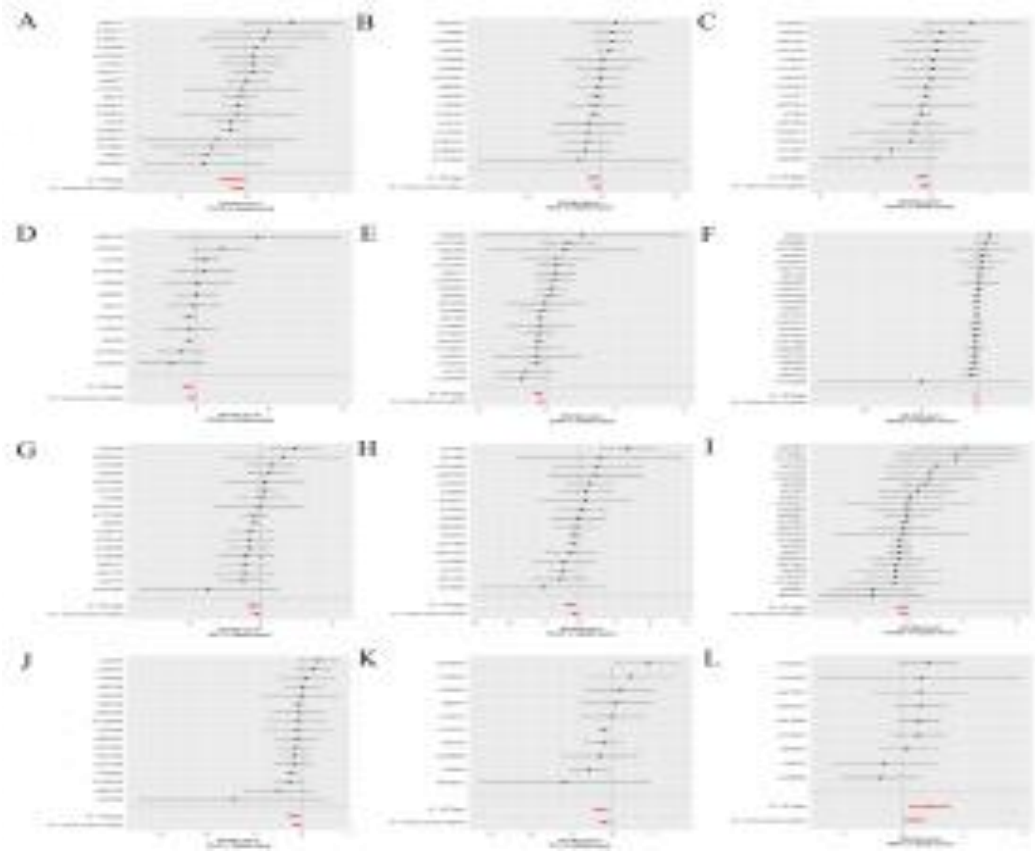

Figure 2. Assessing the relationship between plasma proteins and genetic susceptibility to aplastic anemia based on exposure factor-related instrumental variable evaluation. (A)CCL25. (B)DSG2.

(C)EPHA4. (D)EPHB4. (E)IL3RA. (F)MDGA2. (G)MET. (H)PEAR1. (I)PLXND1. (J)SELE. (K)TLL1. (L)MMP7

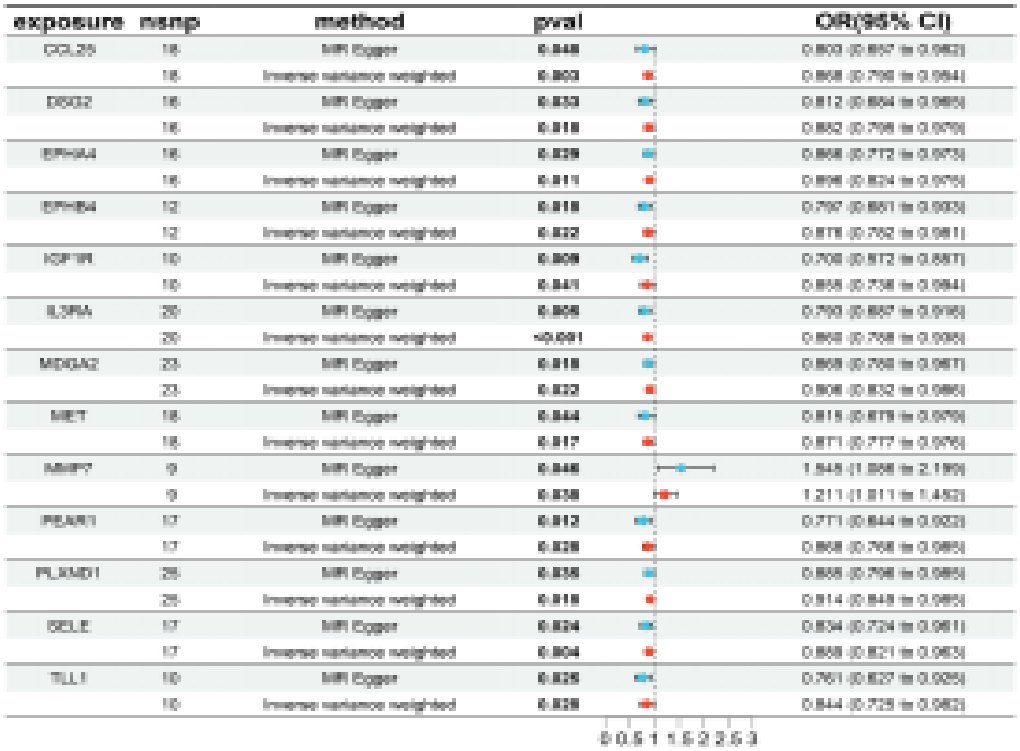

Figure 3. Summarried forest plot of plasma <u>proteins</u> that associated with aplastic anemia.

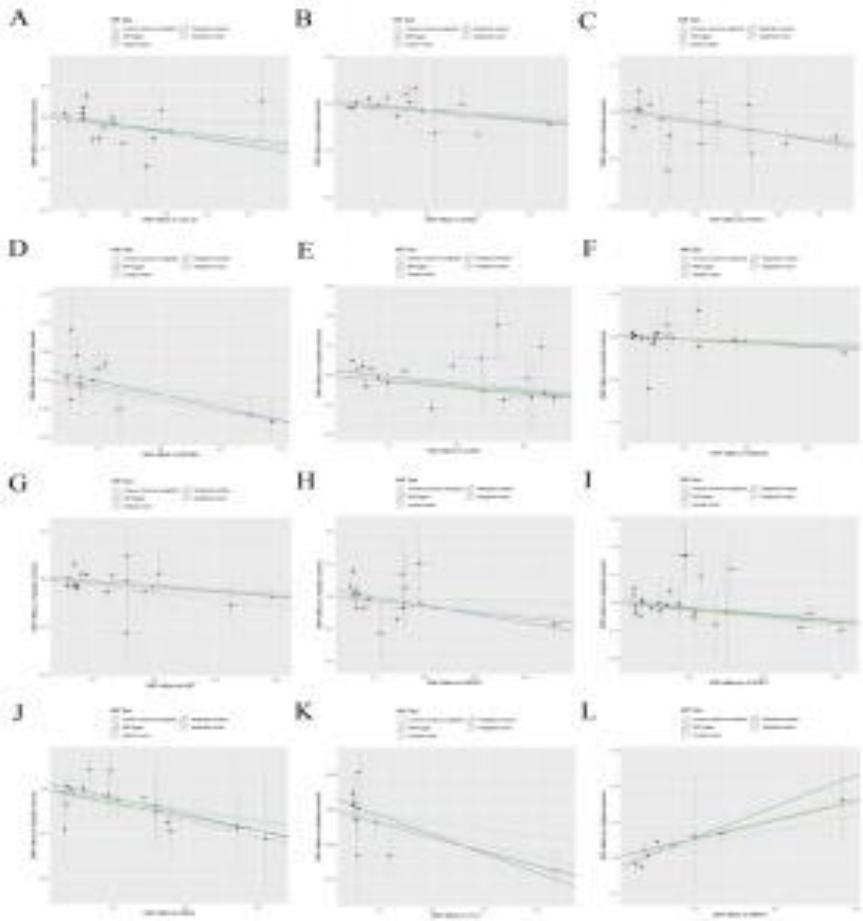

Figure 4. Scatter plot of MR analysis for plasma <u>proteins</u> on genetic susceptibility to AA. (A)CCL25.

(B)DSG2. (C)EPHA4. (D)EPHB4. (E)IL3RA. (F)MDGA2. (G)MET. (H)PEAR1. (I)PLXND1. (J)SELE. (K)TLL1. (L)MMP7. MR, Mendelian randomization; AA, aplastic anemia.

Table 1. The results of MR-Egger intercept analysis.

Exposure	Outcome	Egger_intercept	SE	p value
CCL25	AA	0.015480305	0.016456534	0.360045375
DSG2	AA	0.016182648	0.013700142	0.257199921
EPHA4	AA	0.009830954	0.011628832	0.412106259
EPHB4	AA	0.020073802	0.012684255	0.144600045
IGF1R	AA	0.040565512	0.016269563	0.037327571
IL3RA	AA	0.018919248	0.013966489	0.192299896
MDGA2	AA	0.013852236	0.011125261	0.226804769
MET	AA	0.01196107	0.013110473	0.375137516
PEAR1	AA	0.022651524	0.012976832	0.101335374
PLXND1	AA	0.008429544	0.010093316	0.412218749
SELE	AA	0.015359047	0.014343045	0.301171651
MMP7	AA	-0.030772407	0.019537547	0.159249365
TLL1	AA	0.019118651	0.012624338	0.168379785

Heterogeneity and sensitivity analysis

Cochran's Q test indicated no heterogeneity in the MR analysis results ($p \geq 0.05$) (Table 2 and Figure 5). Sensitivity analysis confirmed the robustness of the MR analysis results (Figure 6).

Table 2. The results of Cochran's Q analysis.

Exposure	Method	Q	Q_df	Q_p val
CCL25	MR Egger	18.72834061	16	0.283001941
DSG2	MR Egger	9.24482353	14	0.815054595
EPHA4	MR Egger	10.58002281	14	0.718667629
EPHB4	MR Egger	10.42729093	10	0.403838328
IL3RA	MR Egger	18.27612622	18	0.437606423
MDGA2	MR Egger	15.4592785	21	0.799221473
MET	MR Egger	19.15246964	16	0.260835934
PEAR1	MR Egger	18.66156071	15	0.229481931
PLXND1	MR Egger	24.20266064	23	0.392658275
SELE	MR Egger	13.0450483	15	0.598818312
TLL1	MR Egger	9.446588676	8	0.306032884
MMP7	MR Egger	2.912013415	7	0.893020614

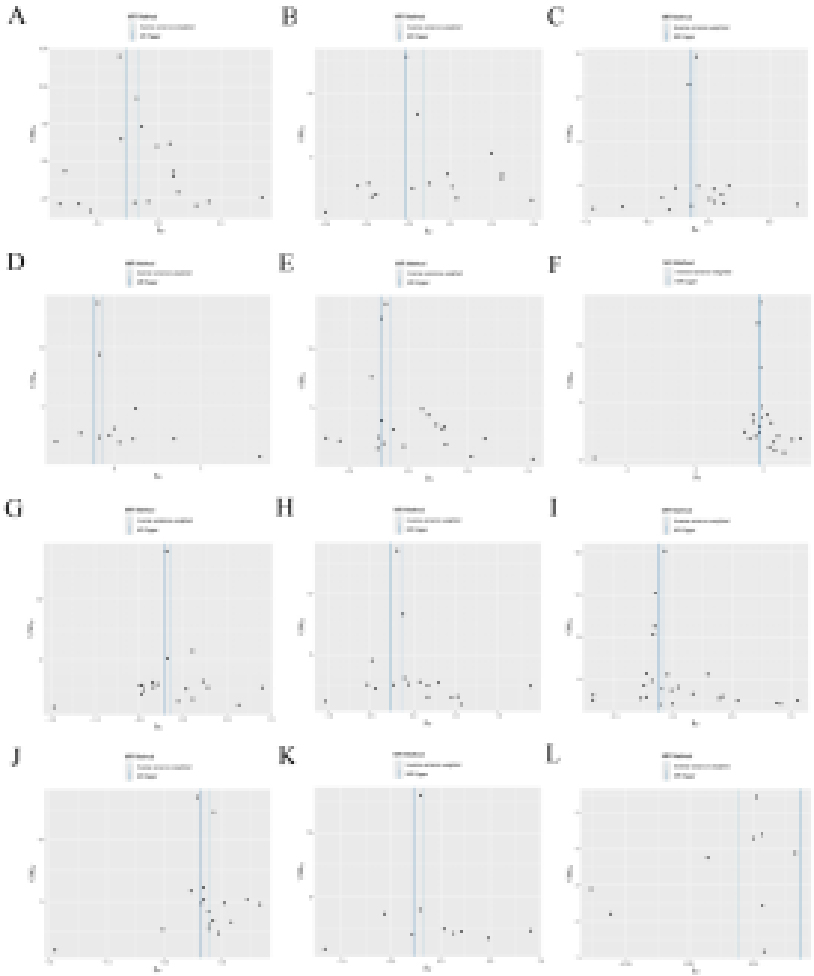

Figure 5. Funnel plot of MR analysis for plasma proteins on genetic susceptibility to AA.(A)CCL25. (B)DSG2. (C)EPHA4. (D)EPHB4. (E)IL3RA. (F)MDGA2. (G)MET. (H)PEAR1. (I)PLXND1. (J)SELE. (K)TLL1. (L)MMP7.

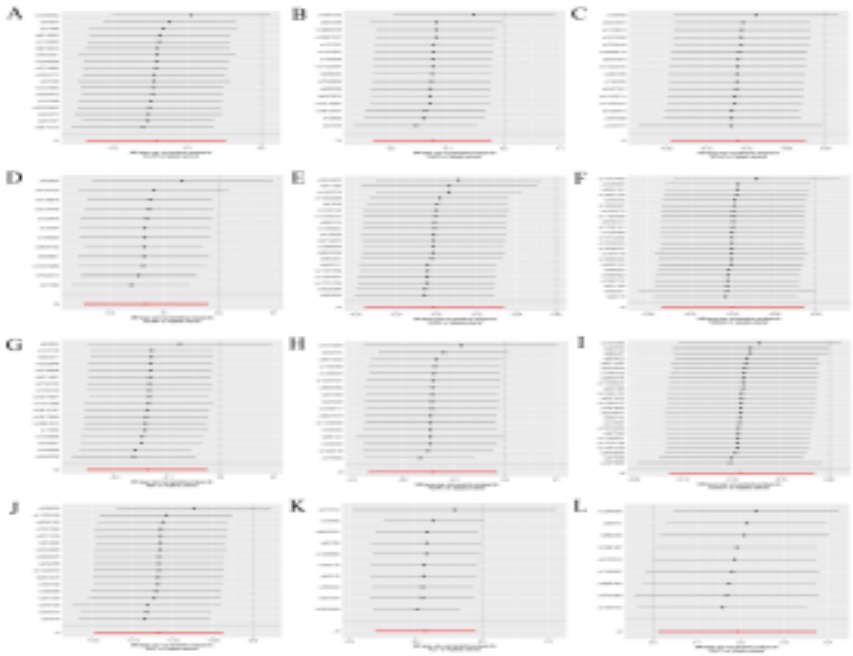

Figure 6. Leave-one-out sensitive analysis for plasma proteins on genetic susceptibility to AA. (A)CCL25. (B)DSG2. (C)EPHA4. (D)EPHB4. (E)IL3RA. (F)MDGA2. (G)MET. (H)PEAR1. (I)PLXND1. (J)SELE. (K)TLL1. (L)MMP7.

Signal pathway

The significant GO analysis of the 12 proteins, including BP, MF, and CC, were showed in Figure 7A. The significant terms of GO-BP were mainly associated with the regulation of GTPase activity, regulation of leukocyte tethering or rolling. The pathways enriched by GO-MF were mainly associated with the transmembrane receptor protein tyrosine kinase activity. The analysis of GO-CC indicated that 12 proteins were significantly enriched in lamellipodium. The KEGG analysis showed that 12 plasma proteins were enriched in Cytokine-cytokine receptor interaction and PI3K-Akt signaling pathway (Figure 7B).

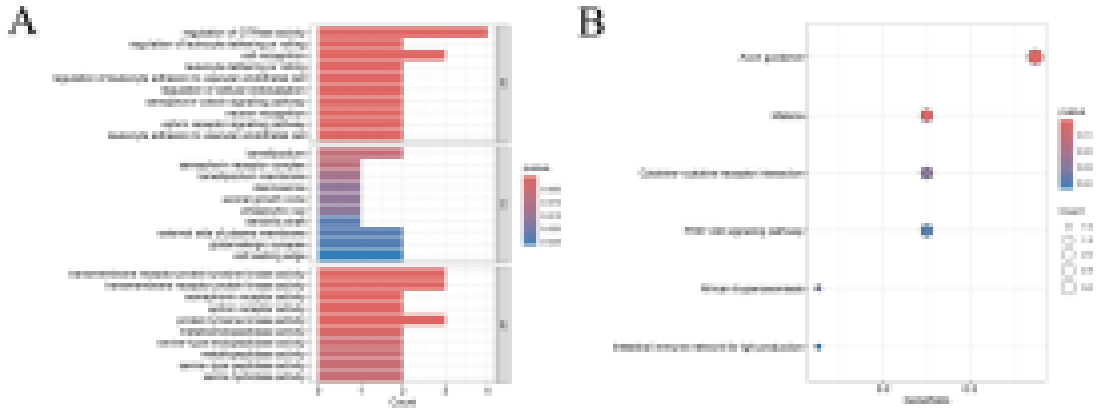

Figure 7. Pathway analysis of AA related plasma proteins. (A)GO annotation. (B)KEGG pathways.

Discussion

In our study, which employed a MR approach, we used data from the Icelandic population to investigate the relationship between 4907 plasma proteins and AA. MR analysis indicated a causal relationship between AA and twelve plasma proteins: CCL25, DSG2, EPHA4, EPHB4, IL3RA, MDGA2, MET, PEAR1, PLXND1, SELE, TLL1, and MMP7. This research lays the foundation for further exploration of AA pathogenesis and provides new evidence for the selection of drug targets for AA treatment.

11 types of plasma proteins were associated with decreased genetic susceptibility to AA, including CCL25, DSG2, EPHA4, EPHB4, IL3RA, MDGA2, MET, PEAR1, PLXND1, SELE, and TLL1. These proteins are widely reported to be closely related to various human diseases. For examples, C-C motif chemokine ligand 25 (CCL25) is primarily expressed in the thymus and intestinal epithelium, and also produced by vascular endothelial cells and other parenchymal cells. It facilitates the migration of immature T cells to the thymus for maturation and release(14). CCL25 binds to CCR9 in a one-to-one manner, participating in various inflammatory diseases and promoting inflammatory responses. Over the years, the role of CCR9/CCL25 in inflammation-related diseases, including cardiovascular diseases, tumors, hepatitis, arthritis, and inflammatory bowel diseases, has become increasingly evident(15-16). These findings suggest that CCR9/CCL25 may be potential targets for various inflammatory diseases. Desmoglein 2 (DSG2) has been associated with various tumors. Yang et al. reported that low DSG2 expression correlates with low survival rates in colon cancer patients, suggesting its potential as a prognostic biomarker for colon cancer(17). Qin et al. found that DSG2 expression is associated with poor prognosis in early cervical cancer(18). EPH receptor A4 (EPHA4) and EPH receptor B4 (EPHB4), members of the ephrin receptor subfamily of the protein tyrosine kinase family, are involved in mediating developmental events and have also been widely reported to be closely related to tumors and stroke(19-22). Research has shown that IL3RA regulates the proliferation, survival, and differentiation of hematopoietic cells and is commonly expressed in acute myeloid leukemia (AML) and classical Hodgkin lymphoma (HL), offering potential for treatment with IL3RA-targeted antibody-drug conjugates(23). IL3RA is also a therapeutic target for primary plasmacytoid dendritic cell

tumors(24). Through Mendelian randomization analysis, Zhang et al. identified that the plasma protein MDGA2 is associated with an increased risk of lung adenocarcinoma(25). Wang et al. described MDGA2 as a key tumor suppressor in gastric cancer, noting that its hypermethylation is an independent prognostic factor for cancer patients(26). The MET proto-oncogene, a receptor tyrosine kinase, has become a prominent molecule in oncology research. High levels of MET amplification and activation of MET mutations or fusions are now recognized as drivers of tumorigenesis, with extensive research focusing on targeted therapies against MET mutations(27-28). Zhang et al. reported that PEAR1 balances intrinsic and extrinsic signals in determining early hematopoietic fate(29). PEAR1 is essential in hemostasis by facilitating platelet adhesion through its extracellular portion, thereby initiating platelet aggregation(30). Research by Li et al. indicates that Plexin D1 negatively regulates the migration of foam cells derived from macrophages through the focal adhesion kinase/Paxillin pathway(31). Chen et al. suggested that Plexin D1 could be a novel target in treating castration-resistant prostate cancer by contributing to neural lineage plasticity(32). Selectin E (SELE) is found in cytokine-stimulated endothelial cells and is implicated in the accumulation of leukocytes at inflammatory sites by mediating cell adhesion to the inner walls of blood vessels(33). Genome-wide association studies have linked variations in TLL1 with the development of hepatocellular carcinoma following the eradication of hepatitis C virus infection(34).

In our study, MMP7 was associated with increased genetic susceptibility to ankylosing spondylitis (AA). According to Briot et al., the overexpression of MMP-7 is directly responsible for the substantial shedding and release of TNF-α from the cytoplasmic membrane in Fanconi anemia(35). Furthermore, MMP7 has been linked to tumor drug resistance and metastasis(36-37).

The pathway analysis showed that 12 plasma proteins were enriched in Cytokine-cytokine receptor interaction and PI3K-Akt signaling pathway. The report of cytokine-cytokine receptor interaction in AA is rather scarce, which may provide a new direction for the research on the related mechanisms of AA. And the PI3K-Akt signaling pathway has been reported in several reports in AA. For example, Formononetin regulates the PI3K/Akt signaling pathway to reverse the Treg/Th17 imbalance in AA mice(38). Panaxadiol saponin improves the ferroptosis in AA mice and Meg-01 cells by activating the PI3K/AKT/mTOR signaling pathway(39).

In summary, our MR study systematically evaluated the causal relationship between plasma protein biomarkers and AA. Characterized by a large sample size, comprehensive proteomic coverage, multilevel bias detection, and extremely low confounding bias, the study identified 12 plasma proteins that are causally related to AA. Future study should focus on validating these findings and developing drugs targeting these potential biomarkers.

Acknowledgements

The authors express their gratitude to Ferkingstad E et al for their invaluable GWAS raw data.

Funding

The present study was supported by the Guangxi natural science foundation of China(2023JJA140185). Scientific Research Project of Guangxi Health and Family Planning Commission(Z20181007). Guangxi Medical and Health Appropriate Technology Development and Promotion Application Project(S2018085). Guangxi Zhuang Autonomous Region Health Commission Key Laboratory of Medical Genetics and Genomics Research Open Project(GXKMGG202304). Guangxi Zhuang Autonomous Region Health Commission self-funded scientific research projects(Z-A20240639).

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the *IEU OpenGWAS project and* deCODE GENETICS.

Ethics approval and consent to participate

Our study is based on open source data, so there are no ethical issues.

Authors' contributions

AGL, YTZ and XWP were responsible for collecting and analyzing data from public datasets, as well as performing statistical analysis. YHL contributed to the conception and design of the study, as well as providing language

modification. All authors have reviewed and approved the final manuscript.

Patient consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

References

1. Giudice V, Selleri C. Aplastic anemia: Pathophy siology. Semin Hematol. 2022;59(1) 13-20.
2. Zhu J, Li W. Role of metabolites in mediating the effect of triacylglycerol on aplastic anemia. Hematology. 2024;29(1):2379178.
3. Yuan S, Titova OE, Zhang K, Gou W, Schillemans T, Natarajan P, et al. Plasma protein and venous thromboembolism: prospective cohort and mendelian rando misation analyses. Br J Haematol. 2023;201 (4):783-92.
4. Ferkingstad E, Sulem P, Atlason BA, Sveinbjornsson G, Magnusson MI, Styrmisdottir EL, et al. Large-scale integration of the plasma proteome with genetics and disease. Nat Genet. 2021;53(12):1712-21.
5. Chen L, Peters JE, Prins B, Persyn E, Traylor M, Surendran P, et al. Systematic Mendelian randomization using the human plasma proteome to discover potential therapeutic targets for stroke. Nat Commun. 2022;13(1): 6143.
6. Yuan S, Xu F, Li X, Chen J, Zheng J, Mantzoros CS, et al. Plasma proteins and onset of type 2 diabetes and diabetic complications: Proteome-wide Mendelian randomization and colocalization analyses. Cell Rep Med. 2023;4(9):101174.
7. Zhang W, Ma L, Zhou Q, Gu T, Zhang X, Xing H. Therapeutic Targets for Diabetic Kidney Disease: Proteome-Wide Mendelian Randomization and Colocalization Analyses. Diabetes. 2024;73(4):618-27.
8. Wang Q, Shi Q, Lu J, Wang Z, Hou J. Causal relationships between inflammatory factors and multiple myeloma: A bidirectional Mendelian randomization study. Int J Cancer. 2022;151(10):1750-9.
9. Chen D, Zhang Y, Yidilisi A, Xu Y, Dong Q, Jiang J. Causal Associations Between Circulating Adipokines and Cardiovascular Disease: A Mendelian Randomization Study. J Clin Endocrinol Metab. 2022;107(6):e2572-e80.
10. Sun Z, Yun Z, Lin J, Sun X, Wang Q, Duan J, et al. Comprehensive mendelian randomize ation analysis of plasma proteomics to identify new therapeutic targets for the treatment of coronary heart disease and myocardial infarction. J Transl Med. 2024;22(1):404.
11. Dang X, Song M, Lv L, Yang Y, Luo XJ. Proteome-wide Mendelian randomization reveals the causal effects of immune-related plasma proteins on psychiatric disorders. Hum Genet. 2023;142(6):809-18.
12. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife. 2018;7.
13. Slob EAW, Burgess S. A comparison of robust Mendelian randomization methods using summary data. Genet Epidemiol. 2020; 44(4):313-29.
14. Tu Z, Xiao R, Xiong J, Tembo KM, Deng X, Xiong M, et al. CCR9 in cancer: oncogenic role and therapeutic targeting. J Hematol Oncol. 2016;9:10.
15. Wu X, Sun M, Yang Z, Lu C, Wang Q, Wang H, et al. The Roles of CCR9/CCL25 in Inflammation and Inflammation-Associated Diseases. Front Cell Dev Biol. 2021;9:686548.
16. Chai S, Wen Z, Zhang R, Bai Y, Liu J, Li J, et al. CCL25/CCR9 interaction promotes the malignant behavior of salivary adenoid cystic carcinoma via the PI3K/AKT signaling pathway. PeerJ. 2022;10:e13844.
17. Yang T, Gu X, Jia L, Guo J, Tang Q, Zhu J, et al. DSG2 expression is low in colon cancer and correlates with poor survival. BMC Gastroenterol. 2021;21(1):7.
18. Qin S, Liao Y, Du Q, Wang W, Huang J, Liu P, et al. DSG2 expression is correlated with poor prognosis and promotes early-stage cervical cancer. Cancer Cell Int. 2020;20:206.
19. Verma M, Chopra M, Kumar H. Unraveling the Potential of EphA4: A Breakthrough Target and Beacon of Hope for Neurological Diseases. Cell Mol Neurobiol. 2023;43(7):33 75-91.
20. Xu LJ, Wang HN, Zhou H, Li SY, Li F, Miao Y, et al. EphA4/ephrinA3 reverse signaling

induced Muller cell gliosis and production of pro-inflammatory cytokines in experimental glaucoma. Brain Res. 2023;1801:148204.
21. Liu C, Han S, Zheng J, Wang H, Li S, Li J. EphA4 regulates white matter remyelination after ischemic stroke through Ephexin-1/ RhoA/ROCK signaling pathway. Glia. 2022; 70(10):1971-91.
22. Piffko A, Uhl C, Vajkoczy P, Czabanka M, Broggini T. EphrinB2-EphB4 Signaling in Neurooncological Disease. Int J Mol Sci. 20 22;23(3).
23. Kirchhoff D, Stelte-Ludwig B, Lerchen HG, Wengner AM, Ahsen OV, Buchmann P, et al. IL3RA-Targeting Antibody-Drug Conjugate BAY-943 with a Kinesin Spindle Protein Inhibitor Payload Shows Efficacy in Preclinical Models of Hematologic Malignancies. Cancers (Basel). 2020;12(11).
24. Pelosi E, Castelli G, Testa U. CD123 a Therapeutic Target for Acute Myeloid Leukemia and Blastic Plasmocytoid Dendritic Neoplasm. Int J Mol Sci. 2023;24(3).
25. Zhang L, Xiong Y, Zhang J, Feng Y, Xu A. Systematic proteome-wide Mendelian randomization using the human plasma proteome to identify therapeutic targets for lung adenocarcinoma. J Transl Med. 2024; 22(1):330.
26. Wang K, Liang Q, Li X, Tsoi H, Zhang J, Wang H, et al. MDGA2 is a novel tumour suppressor cooperating with DMAP1 in gastric cancer and is associated with disease outcome. Gut. 2016;65(10):1619-31.
27. Guo R, Luo J, Chang J, Rekhtman N, Arcila M, Drilon A. MET-dependent solid tumours - molecular diagnosis and targeted therapy. Nat Rev Clin Oncol. 2020;17(9):569-87.
28. Spitaleri G, Trillo Aliaga P, Attili I, Del Signore E, Corvaja C, Corti C, et al. MET in Non-Small-Cell Lung Cancer (NSCLC): Cross 'a Long and Winding Road' Looking for a Target. Cancers (Basel). 2023;15(19).
29. Zhang S, Qu K, Lyu S, Hoyle DL, Smith C, Cheng L, et al. PEAR1 is a potential regulator of early hematopoiesis of human pluripotent stem cells. J Cell Physiol. 2023;238(1):179-94.
30. Ansari N, Najafi S, Shahrabi S, Saki N. PEAR1 polymorphisms as a prognostic factor in hemostasis and cardiovascular diseases. J Thromb Thrombolysis. 2021;51(1):89-95.
31. Li C, Niu Y, Chen J, Geng S, Wu P, Dai L, et al. Plexin D1 negatively regulates macrophage -derived foam cell migration via the focal adhesion kinase/Paxillin pathway. Biochem Biophys Res Commun. 2024;725:150236.
32. Chen B, Xu P, Yang JC, Nip C, Wang L, Shen Y, et al. Plexin D1 emerges as a novel target in the development of neural lineage plasticity in treatment-resistant prostate cancer. Oncogene. 2024;43(30):2325-37.
33. Purdy M, Obi A, Myers D, Wakefield T. P- and E- selectin in venous thrombosis and non-venous pathologies. J Thromb Haemost. 2022; 20(5):1056-66.
34. Matsuura K, Sawai H, Ikeo K, Ogawa S, Iio E, Isogawa M, et al. Genome-Wide Association Study Identifies TLL1 Variant Associated With Development of Hepatocellular Carcinoma After Eradication of Hepatitis C Virus Infection. Gastroenterology. 2017;152 (6):1383-94.
35. Briot D, Mace-Aime G, Subra F, Rosselli F. Aberrant activation of stress-response pathways leads to TNF-alpha oversecretion in Fanconi anemia. Blood. 2008;111(4):1913-23.
36. Ou S, Chen H, Wang H, Ye J, Liu H, Tao Y, et al. Fusobacterium nucleatum upregulates MMP7 to promote metastasis-related character ristics of colorectal cancer cell via activating MAPK(JNK)-AP1 axis. J Transl Med. 2023; 21(1):704.
37. Yuan JQ, Zhang KJ, Wang SM, Guo L. YAP1/MMP7/CXCL16 axis affects efficacy of neoadjuvant chemotherapy via tumor environment immunosuppression in triple-negative breast cancer. Gland Surg. 2021;10 (9):2799-814.
38. Lan H, Qiu W, Wu J, Hu Z, Zhang X, Zhu L. Formononetin reverses Treg/Th17 imbalance in immune-mediated bone marrow failure mice by regulating the PI3K/Akt signaling pathway. Chin Med. 2024; 25;19(1):55.
39. Liu W, Tan Z, Zhao Y, Zhao Y, Yu X, Wang B, et al. Panaxadiol saponin ameliorates ferroptosis in iron-overload aplastic anemia mice and Meg-01 cells by activating Nrf2/HO-1 and PI3K/AKT/mTOR signaling pathway. Int Immunopharmacol. 2023; 118:110131.