Characterization of the human ABO genotypes and their association to common inflammatory and cardiovascular diseases in the UK Biobank

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Abstract
The ABO gene contains three major alleles that encode different antigens; A, B, and O, which determine an individual’s blood group. Previous studies have primarily focused on identifying associations between ABO blood groups and diseases risk. Here, we sought to test for association between ABO genotypes (OO, OA, AA; OB, BB, and AB) and a large set of common inflammatory and cardiovascular diseases in the UK Biobank as well as disease-related protein biomarkers in NSPHS. We first tested for association by conducting a likelihood ratio test, testing whether ABO contributed significantly to the risk for 24 diseases, and 438 plasma proteins. For phenotypes with FDR < 0.05, we tested for pair-wise differences between genetically determined ABO genotypes using logistic or linear regression. Our study confirmed previous findings of a strong association between ABO and cardiovascular disease, identified associations for both type 1 and type 2 diabetes, and provide additional evidence of significant differences between heterozygous and homozygous allele carriers for pulmonary embolism, deep vein thrombosis, but also for von Willebrand factor levels. Furthermore, the results indicated an additive effect between genotypes, even between the two most common A subgroups, A1 and A2. Additionally, we found that ABO contributed significantly to 39 plasma proteins, of which 23 have never been linked to the ABO locus before. These results show the need of incorporating ABO genotype information in the consultation and management of patients at risk, rather than classifying patients into blood groups.

1 | INTRODUCTION

The ABO blood group antigens were first identified by Karl Landsteiner in the beginning of the twentieth century, and its alleles give rise to the four major blood groups A, B, AB, and O. Since then, numerous associations have been reported between particular ABO blood groups and an increased susceptibility to disease, ranging from cardiovascular diseases to infections. It has been shown that individuals with an O blood group have a lower risk of cardiovascular diseases, including thromboembolism,1–3 pulmonary embolism (PE),3,4 and possibly also for myocardial infarction (MI),3 compared to other blood groups. The different blood groups (A, B, AB, and O) have different properties where, for example, persons with an O blood group are less prone to coagulation, possibly since they express significantly
lower plasma levels of both coagulation factor VIII (FVIII) and von Willebrand factor (vWF). Elevated levels of both vWF and FVIII have been associated with risk of cardiovascular disease, whereas a deficiency of vWF is what gives rise to the most commonly inherited human bleeding disorder - von Willebrand disease. This agrees with an increased risk of bleeding and reduced incidence of vascular occlusion for individuals with an O blood group.

 Associations have also been found with inflammatory responses such as allergies, however with somewhat conflicting results. Generally, individuals with blood group O have been suggested to have greater susceptibility to asthma and allergic rhinitis, although there are some contradictory findings. In contrary, most studies seem to agree on a higher risk of developing atopic dermatitis for non-O individuals. In a recent study, a significant difference in prevalence between blood groups was also suggested in rheumatic diseases where spondyloarthropathy, vasculitis, and rheumatic arthritis were more common in patients with blood group A and systemic lupus erythematosus and systemic sclerosis were more common in patients with blood group O.

The blood groups are determined by the ABO gene located at chromosome 9. Note, ABO encodes a galactosyltransferase with a function to convert a precursor fucosyltransferase H antigen (encoded by FUT1 when expressed on red blood cells, and by FUT2 when found in secretions) to a mature antigen via sugar donation. The proteins responsible for this conversion are encoded by the A and B alleles, synthesizing the A and B antigen, respectively. The O allele encodes an enzymatically inactive protein product, leaving the H antigen as is (referred to as the O antigen). Individuals with blood group AB will therefore have both A and B antigens while individuals with blood group O will have neither. These three ABO alleles - A, B, and O - were long thought to be all, but since the blood grouping system started to become more systematically investigated, several sub-alleles and minor alleles have been found. One example is the A1 and A2 sub-alleles where both encodes GTA, but with a much lower enzyme activity for ABO allele A2 than for A1. Consequently, A2 individuals have a lower expression of the A antigen.

Apart from being expressed on red blood cells, the ABO antigens are also expressed on other types of cells, mostly epithelial and endothelial cells, and are therefore also termed histo-blood group antigens. In approximately 80% of the population, carrying the FUT2 encoded secretor type, the ABO antigens are also secreted in bodily fluids, such as saliva, where they are residing on mucins. Consequently, 20% of the population has a non-functional FUT2 gene and does not secrete ABO antigens in other bodily fluids. These blood group antigens play a role in cell-cell recognition, and thus, it is imaginable that these antigens might serve as potential receptors for either microorganisms or toxins and allergens.

However, as ABO is also expressed on vWF, it might be the link to how ABO influence plasma levels of vWF and FVIII. vWF acts as a carrier for FVIII, which localizes FVIII to the site of possible vascular injury. Also, ABO has been associated to levels of inflammatory proteins in coronary artery syndrome, as well as other important factors in the coagulation cascade, such as soluble tissue factor, sTF. Further on, we and others have previously found ABO to be associated with a large set of putative biomarkers for inflammation and cardiovascular diseases in genome wide association studies (GWAS), including the levels of, for example, vascular endothelial growth factor receptor 2 (VEGFR-2), angiopeptin-1 receptor (TIE2), platelet endothelial cell adhesion molecule (PECAM-1) and E-selectin.

As of yet, the biological function of the blood groups is not fully understood. The vast majority of studies have focused on the blood groups A, B, AB, and O, but very little attention has been paid to the underlying dose effect that might arise between individuals of blood group A and B being homozygous (AA or BB) or heterozygous (AO or BO). Also, the heterogeneity in effects, where different ABO alleles are risk alleles for different diseases, has not been a focus for previous studies. Therefore, there is a need to systematically examine ABO genotype associations in common cardiovascular and inflammatory diseases. Here, we therefore aim to extend current knowledge on ABO blood group associations by a detailed analysis of ABO genotypes. The goal is (1) to evaluate potential differences in susceptibility to common cardiovascular and inflammatory diseases between heterozygous and homozygous individuals and (2) to link ABO associations to biological mechanisms by comparing the ABO effects between the diseases to the ABO effects on a large set of disease-related plasma proteins. As previous associations to inflammatory diseases and reactions have been conflicting with inconclusive results, we decided to focus on these phenotypes, with the aim to try to disentangle previous associations, using associations with strong support (such as vWF, DVT and PE) as proof of concept. We have tested for association with 17 inflammatory and seven cardiovascular diseases, as well as over 400 proteins that have previously been highlighted as potential biomarkers for different diseases. As an individual's blood group seem to play a quite substantial role in disease susceptibility, a better characterization can aid clinicians in consulting and managing patients at risk. By analyzing diseases and plasma protein levels jointly, we have the possibility to extend to biological mechanisms beyond disease status.

2 | METHODS

2.1 | Study cohort and assessment of disease status

2.1.1 | UK Biobank

The UK Biobank (UKB) recruited 502,682 individuals, aged 37–73 years at recruitment, from across the UK during 2006–2010. Participants were interviewed about lifestyle and disease history via touchscreen questionnaires and verbal interviews. Genotyping has been performed in UKB using two different custom-designed microarrays, UK BILEVE and Axiom. These contain 807,411 and 820,967 SNPs, respectively, and overlap with 95% common content.
Imputation of over 90 million SNPs was performed using UK10K and 1000 genomes phase 3 as reference panels. Imputations from the third release of imputed data from UKB (accessed March 2018), was used in the current study. Before analysis, participants were filtered for genotype call rate (>95%), high heterozygosity and sex discrepancies between self-reported and genetic sex. This leaves 487 409 individuals available for analysis. Additionally, as a sensitivity analysis to minimize the effects of population stratification, unrelated participants (pairwise kinship >0.044), self-reported as of white British descent and classified as Caucasian by principal component analysis were selected, to have as high statistical power as possible. This resulted in 17 inflammatory and seven cardiovascular diseases. Data taken from the registries were categorized according to International Classification of Diseases (ICD), revision nine (ICD-9) and 10 (ICD-10). A detailed description of all data-fields and coding used for each disease and disease status can be found in Table S1. All participants were assigned their respective ABO genotype (Table S2), based on three ABO gene allele-defining variants: rs8176746 (Leu266Met), rs8176747 (Gly268Ala),17 and the O blood type causing deletion rs8176719 (261DelG).26 Furthermore, to examine whether there was a difference in risk between the most common A2 allele, into A1 and A2, additional regression analyses were performed in UKB after having subtyped all individuals carrying at least one A allele, into A1 and A2, using the variant rs1053878:C:T,33 where the C allele tags the T allele (Table S3). The test statistic is given by the difference in residual deviance between the null and the full model, divided by the residual variance. As assuming overdispersion in the logistic modeling, the test statistic is chi-squared-distributed with five degrees of freedom. Correction for multiple testing was done using a false discovery rate (FDR) of < 0.05. Then, for all diseases and proteins that passed the likelihood ratio test, that is, still had a significant association after FDR correction, the discovery rate (FDR) of < 0.05. Then, for all diseases and proteins that passed the likelihood ratio test, that is, still had a significant association after FDR correction, the ABO genotypes were tested pair-wisely in a logistic or linear regression. In these tests, a p value of < 0.01 was considered significant adjusting for five independent tests, as the remaining 10 pair-wisely tested genotypes are dependent on the first five. When the division of A into A1 and A2 was considered, we used a corrected significance threshold of p < 0.006 (0.05/9) to adjust for nine independent tests, as the remaining are dependent on the first nine. Graphs and analyses were made using the rpart, ggplot2, cowplot, gridExtra, egg, and broom packages. To construct ABO genotypes, individuals were haplotyped using haplo-stats in R.

2.2 Statistical analyses

All statistical analyses were performed using R v3.6.3.32 All diseases were analyzed with logistic regression, and proteins with linear regression, using the glm function, including age, sex, smoking status, body mass index (BMI), and the five first genetic principal components as covariates. For comparability reasons between the analyses, we decided to use the same regression model throughout all phenotypes, and at the same trying to avoid including colliders or adjusting for mediators affected by unmeasured or unknown factors. ABO genotypes were analyzed as a six-level factor (OO, OA, AA, OB, BB, AB) variable. First, to test whether ABO genotypes were associated with disease or plasma protein levels, we assessed their total contribution to the regression model by a likelihood ratio test. This was done by comparing a null model, including only the covariates, with the full model, also including the ABO genotype. The test statistic is given by the difference in residual deviance between the null and the full model, divided by the residual variance. Assuming no over dispersion in the logistic modeling, the residual variance was fixed to one. Only in the linear modeling of the biomarkers, the residual variance was allowed to vary. Under H0, this test statistic is chi-squared-distributed with five degrees of freedom. Correction for multiple testing was done using a false discovery rate (FDR) of < 0.05. Then, for all diseases and proteins that passed the likelihood ratio test, that is, still had a significant association after FDR correction, the ABO genotypes were tested pair-wisely in a logistic or linear regression. In these tests, a p value of < 0.01 was considered significant adjusting for five independent tests, as the remaining 10 pair-wisely tested genotypes are dependent on the first five. When the division of A into A1 and A2 was considered, we used a corrected significance threshold of p < 0.006 (0.05/9) to adjust for nine independent tests, as the remaining are dependent on the first nine. Graphs and analyses were made using the rpart, ggplot2, cowplot, gridExtra, egg, and broom packages. To construct ABO genotypes, individuals were haplotyped using haplo-stats in R.
2.3 | Ethics committee approval

The UKB resource was given ethical approval by the North West Multicentre Research Ethics Committee (covering the United Kingdom), National Information Governance Board for Health and Social Care (covering England and Wales) and Community Health Index Advisory Group (covering Scotland). The UKB possesses a generic Research Tissue Bank approval granted by the National Research Ethics Service. This approval lets applicants conduct research on UKB data without having to obtain separate ethical approvals. Additionally, the UKB study was approved by the National Research Ethics Committee (REC reference 11/NW/0382). Informed consent to the study was given by all participants. An application for using data from UKB has been approved (application nr: 8260). The UKB analysis performed in this study has also been approved by the Swedish Ethical Review Authority (dnr: 2020-04415).

The NSPHS was approved by the local ethics committee at the University of Uppsala (Regionala Etikprövningsnämnden, Uppsala, 2005:325, and an extension of the project was approved 2016-03-09) in compliance with the declaration of Helsinki. Informed consent to the study was given by all participants, including the examination for environmental and genetic cause of disease. If a person was not of age (< 18 years), a legal guardian signed additionally.

3 | RESULTS

3.1 | ABO genotypes in UK Biobank and Northern Swedish Population Health Study

For a majority of the UKB participants, 487 269 out of 487 409, we were able to resolve the haplotypes and construct ABO genotypes (Table 1). The most common genotype was OO (43.3%), followed by AO (35.9%), BO (9.0%), AA (7.5%), AB (3.6%) and BB (0.6%). A total of 140 individuals had an undefined ABO genotype. In the sensitivity analysis, including unrelated British Caucasians, we were able to resolve the haplotypes for 361 880 out of 361 975 participants, and the most common genotype was OO (43.5%), followed by AO (37%), BO (8.0%), AA (7.8%), AB (3.3%), and BB (0.4%). Here, a total of 95 individuals had an undefined ABO genotype, due to lacking critical genotypes, and were thus excluded from further analyses (see Table S4). In NSPHS, we were able to resolve the haplotypes and construct ABO genotypes for all 867 participants (Table 1, Table S5). Here, the most common genotype was AO (36.1%), followed by OO (32.6%), AA (13.6%), BO (10.7%), AB (5.2%), and BB (1.7%). When subclassifying the UKB into A1 and A2 genotypes, we were able to resolve the haplotypes and construct ABO genotypes for 483 314 out of the 487 409 individuals, resulting in the most common genotype being OO (43.1%), followed by A1O (27.1%), A2O (9.0%) and BO (9.0%), A1A1 (4.2%), A1A2 (2.8%), A1B (2.7%), A2B (0.9%), BB (0.6%) and A2A2 (0.5%) being the most uncommon (Table 1). Due to the much smaller sample size, further subclassification into A1 and A2 was not performed in the NSPHS.

3.2 | Association of ABO genotypes on disease

In the likelihood ratio test, ABO genotypes were associated with DVT, PE, MI, type 2 diabetes (T2D) and type 1 diabetes (T1D) after adjusting for multiple testing (FDR < 0.05, Table S6). Differences (Table S7) between pair-wise ABO genotypes could also be seen for the same diseases (Figures 1 and 2A–D, with results from the sensitivity analysis in Figures S1 and S2). A description of the covariates and their effects on the respective diseases can be found in Tables S8 and S9.

### Table 1 ABO genotype frequencies in the two study populations

| ABO genotype | UKBsens | UKBfull | UKBsens | UKBfull | NSPHS |
|--------------|---------|---------|---------|---------|-------|
|              | N carriers | N carriers | Frequency | N carriers | Frequency | N carriers | Frequency |
| AA           | 28 130    | 36 402   | 0.078    | 0.075    | 118    | 0.136 |
| A1A1         | 20 534    | 0.042    |
| A1A2         | 13 438    | 0.028    |
| A2A2         | 2430      | 0.005    |
| AO           | 134 003   | 174 526  | 0.370    | 0.361    | 45     | 0.052 |
| A1O          | 131 039   | 0.271    |
| A2O          | 43 487    | 0.090    |
| AB           | 12 032    | 17 632   | 0.033    | 0.036    | 15     | 0.017 |
| A1B          | 13 122    | 0.027    |
| A2B          | 4508      | 0.009    |
| BB           | 1324      | 28 498   | 0.004    | 0.006    | 313    | 0.361 |
| BO           | 28 864    | 43 579   | 0.080    | 0.090    | 93     | 0.107 |
| OO           | 157 527   | 208 328  | 0.435    | 0.431    | 283    | 0.326 |

*aUKB sensitivity analysis, that is, including only the participants who have self-identified as white British Caucasian and being clustered together based on genetic principal components, N = 361 975.

*bUKB full cohort, N = 487 409.
Results from the regression analysis for all diseases where ABO contributed significantly to the association. Based on the full UKB cohort. All diseases are stated on the y axis, the ABO genotype comparison is stated on the x axis with their respective ratio. For visualization purposes, the diseases have been clustered with hierarchical clustering by their respective odds ratios. Odds ratios for each disease and ABO genotype comparison are shown within each square. Squares are colored by Z-score, where blue depicts a negative Z-score and red a positive Z-score. Significance thresholds correspond to: p < 0.05 = ·; p < 0.01 = *, p < 0.001 = **, p < 0.0001 = ***

For T2D, homozygous OO was associated with a decreased risk. However, when restricting the analysis to the unrelated British Caucasian, the results did not remain significant, which makes the results uncertain as it can be either stemming from an increased sample size, or the introduction of population stratification (Figure S3A,B). For T1D, being a homozygous carrier for the B allele was associated with higher odds of disease (ORBB/OO 1.78 [95% CI 1.28–2.39], p = 0.001; and ORBB/BO 1.63 [95% CI 1.16–2.21], p = 0.003; Figure 2A) For DVT, PE, and MI, the OO genotype was associated with lower odds of disease (Figure 2B–D), which is in line with previous studies, where the O blood group is protective. In addition, for DVT, significantly higher odds were identified in homozygous A allele carriers (AA) than for heterozygous (AO) individuals (ORAA/OO 1.17 [95% CI 1.10–1.25], p < 0.001; Figure 2C). Having an AB genotype also significantly increased the odds for DVT compared to heterozygous A (AO), and a nominally significant higher odd for homozygous B allele carriers (BB) compared to heterozygous carriers (BO). Similar patterns could be seen for PE, suggesting an additive effect of being a heterozygous or homozygous carrier compared to having an OO genotype (Figure 2D).

Additionally, the heterozygous effect persists even when subclassifying A allele carriers into A1 and A2. A significant difference in risk is seen both for genotype A1O in comparison to A2O (PE: ORA1O/A2O 1.37 [95% CI 1.25–1.51], p < 0.001; DVT: ORA1O/A2O 1.34 [95% CI 1.24–1.44], p < 0.001) and A1A1 in comparison to A2A2 (PE: ORA1A1/A2A2 2.03 [95% CI 1.38–3.12], p < 0.001; DVT: ORA1A1/A2A2 1.46 [95% CI 1.12–1.95], p = 0.008), as well as A1O (PE: ORA1A1/A1O 1.21 [95% CI 1.09–1.35], p < 0.001; DVT: ORA1A1/A1O 1.19 [95% CI 1.10–1.30], p < 0.001) and A2O (PE: ORA1A1/A2O 1.67 [95% CI 1.47–1.90], p < 0.001; DVT: ORA1O/A2O 1.60 [95% CI 1.44–1.76], p < 0.001; Table S10). This pattern is apparent both for DVT and PE (Figure S4).

### 3.3 Association of ABO to plasma protein levels

To link identified disease associations to biological mechanisms, we performed similar analyses in relation to the level of plasma proteins, where a majority are putative biomarkers for cardiovascular and inflammatory diseases. Note, ABO contributed to the association of 39 out of 438 proteins tested (Table 2, Table S11). Of these, 23 have never been associated to ABO before (with extended references in Table S12, and protein function descriptions in Table S13). The effect of all covariates on the respective proteins from the main regressions can be found in Table S14. For the majority of proteins, those of blood group A tend to be associated with lower levels, compared to both blood group B and O, and blood group B proteins tend to be associated with higher levels also compared to O, in a relation most similar to AA < AO < OO < AB < BO < BB (Figure S5,
For some proteins, an association pattern more similar to that of the cardiovascular diseases of $OO < BO < BB < AB < AO < AA$ was observed. One notable example is vWF, where all non-O blood groups are associated with higher plasma levels. For vWF, a nominally significant difference between a heterozygous (AO) and homozygous (AA) A allele carriers could also be seen (Figure 2E). Similarly, to the diseases, differences in heterozygous and homozygous A and B allele carriers could be seen for some proteins. However, in contrary to the disease-related analyses where A and B alleles often had the same direction of effect in relation to the O allele (Figure 2B–D), the effect of A and B alleles were in the opposite direction compared to O for several proteins (either $A < O < AB < B$ as mentioned above, or $B < AB < O < A$; Figure S5, Figures S6–S44). For example, PECAM-1 levels were significantly lower among individuals with AA or AO genotypes compared to OO, whereas the levels were significantly higher among individuals with BB or BO genotypes compared to OO (Figure 2F). This difference persists in the A vs B specific comparisons, with significantly...
| Disease (UKB)               | N cases/N controls\(^a\) | \(p\) value | FDR   |
|-----------------------------|---------------------------|-------------|-------|
| Deep vein thrombosis       | 11 826/473 031            | < 0.001     | < 0.001 |
| Pulmonary embolism         | 7027/477 830              | < 0.001     | < 0.001 |
| Myocardial infarction      | 16 070/468 787            | < 0.001     | < 0.001 |
| Type 2 Diabetes\(^b\)      | 23 206/453 390            | < 0.001     | 0.001  |
| Type 1 Diabetes\(^b\)      | 3575/481 282              | 0.004       | 0.026  |
| Hypertension               | 93 122/391 735            | 0.017       | 0.083  |
| Atherosclerosis            | 1497/483 360              | 0.026       | 0.103  |
| Gout                       | 9070/475 787              | 0.055       | 0.188  |
| Ischemic stroke            | 7934/476 923              | 0.122       | 0.324  |
| Hay fever                  | 31 014/453 843            | 0.112       | 0.324  |
| Esophagitis                | 11 839/473 018            | 0.231       | 0.514  |
| Ulcerative colitis         | 2356/482 501              | 0.236       | 0.514  |
| Asthma                     | 64 006/420 851            | 0.262       | 0.524  |
| Appendicitis               | 5182/479 675              | 0.299       | 0.552  |
| Eczema                     | 17 047/467 810            | 0.326       | 0.559  |
| Osteoarthritis             | 76 375/408 482            | 0.399       | 0.639  |
| Psoriasis                  | 2569/482 288              | 0.448       | 0.671  |
| IBD                        | 6516/478 341              | 0.506       | 0.715  |
| Inflammatory polyarthropathies | 21 781/463 076          | 0.596       | 0.759  |
| Ankylosing spondylitis     | 1639/483 218              | 0.601       | 0.759  |
| Celiac disease             | 2075/482 782              | 0.706       | 0.847  |
| Crohn's disease            | 4565/480 292              | 0.767       | 0.877  |
| Psoriatic arthropathy      | 1334/483 523              | 0.874       | 0.920  |
| Rheumatoid arthritis       | 8183/476 674              | 0.912       | 0.920  |
| **Protein/Panel (NSPHS)\(^c\)** | **N\(^d\)**               |             |       |
| CDH5/CVD III               | 856                       | < 0.001     | < 0.001 |
| ICAM-2/CVD III             | 856                       | < 0.001     | < 0.001 |
| PECAM-1/CVD III            | 856                       | < 0.001     | < 0.001 |
| SEL/E/CVD III              | 856                       | < 0.001     | < 0.001 |
| TIE2/CVD II                | 837                       | < 0.001     | < 0.001 |
| CTRC/CVD II                | 837                       | < 0.001     | < 0.001 |
| PODXL/ONC II               | 819                       | < 0.001     | < 0.001 |
| Gal-4/CVD III              | 856                       | < 0.001     | < 0.001 |
| TF/CVD II                  | 837                       | < 0.001     | < 0.001 |
| vWF/CVD III                | 856                       | < 0.001     | < 0.001 |
| CD200/NEU I                | 814                       | < 0.001     | < 0.001 |
| EPHB4/CVD III              | 849                       | < 0.001     | < 0.001 |
| CCL25/INF I                | 857                       | < 0.001     | < 0.001 |
| IFN-gamma-R1/CVD II        | 819                       | < 0.001     | < 0.001 |
| GDNFR-alpha-3/NEU I        | 814                       | < 0.001     | < 0.001 |
| TM/CVD II                  | 837                       | < 0.001     | < 0.001 |
| ITGB5/CVD II               | 819                       | < 0.001     | < 0.001 |
| CA9/CVD II                 | 814                       | < 0.001     | < 0.001 |
| IL-18BP/CVD III            | 856                       | < 0.001     | < 0.001 |
| DLK-1/CVD III              | 856                       | 0.001       | 0.011  |
increased protein levels even for the AB genotype in comparison to both the AO and AA genotypes.

4 | DISCUSSION

We have determined the ABO genotype in participants of two large, population-based cohorts. In contrast to most previous studies, we have investigated genotypes rather than the ABO blood group phenotype. Variation at genotype level at the ABO locus influenced the risk for five out of the 24 diseases analyzed in UK Biobank. So, ABO was associated with common cardiovascular disease, in agreement with previous studies. In addition, we also found a significant association with T1D that has not previously been reported. Furthermore, 39 putative biomarkers were associated to variation at the ABO locus. Of these, 23 associations have not previously been reported, neither at locus-level or at the level of individual ABO genotypes. Additionally, many confirmed previous associations, like the coagulation linked proteins vWF, and tissue factor (TF), thrombomodulin (TM), and the association to E-selectin (SELE).

A previous study in UKB investigated the association between disease and health related traits, mainly cardiovascular disease and traits related to cardiovascular health, by comparing A, B, and O individuals using the same genetic variants for genetic determination of the blood groups, namely rs8176746, rs8176747 and rs8176719. In our current study, we increase the spectrum of diseases, by extending to inflammatory disease, as well as including all ABO genotypes instead of only the A, B, and O groups, aiding as an extension of previously published data. Our main analyses were performed on all UKB participants, including 487,409 participants. As a sensitivity analysis, we then included only unrelated participants who had self-identified as white British and been classified as Caucasians on genetic principal component analyses (N = 361,975). Results between main and sensitivity analyses were all consistent, except for T2D, indicating that we gain power by including all participants without introducing bias or spurious associations stemming from population stratification. Since the majority of the participants are British Caucasians; our results are mainly applicable to European populations and should be interpreted with care in relation to non-European populations.

4.1 | Diseases and coagulation

Our findings for cardiovascular diseases are consistent with previous studies, where blood group O-individuals have lower risk of
developing vascular occlusion. In addition to previous studies, we were also able to discern a difference between the individual genotypes. Large effects were seen for DVT and PE, which are both linked to high coagulation activity. For these diseases we could clearly see that there was a big difference between heterozygous (AO and BO) and homozygous (AA and BB) individuals. This effect was also seen between different A subtype carriers, both for homozygous (A1A1, A1A2 and A2A2) and heterozygous (A1O and A2O) A allele carriers. Here, the effect seems to be additive, with homozygous carriers of A or B posing a larger risk than heterozygous carriers with one O allele. The different genotype effects were all similar for DVT and PE, where the risk was lowest among OO < AO ~ BO < AB--AA--BB. This suggests that the causal mechanisms for ABO on these diseases are most likely through the same pathway(s). This also agrees with the underlying disease mechanism, where part or all of the deep vein thrombus is dislodged and transported through the right side of the heart before arresting in the pulmonary vasculature causing PE. A recent study by Goumell and colleagues, assessed the risk of venous thrombosis (VT) in relation to ABO genotypes, and subclassified A into A1 and A2 and O into O1 and O2 respectively. They found a difference in risk between A1 and A2, where only A1 is posing an increased risk for VT compared to O, and not A2 that only showed a trend toward a moderately increased risk. They further emphasized the need of using ABO haplotypes to accurately estimating the risk of VT attributable to ABO. We were able to replicate these results for DVT and VT, where A2 seems to be the driving allele in risk attributed to the A allele(s) (Figure 54). Furthermore, B seems to be the driving allele in increased risk for individuals with an A2B genotype.

Several of the proteins that were associated with ABO genotypes have previously been linked to coagulation. As for DVT and PE, we found moderate differences in the levels of vWF between heterozygous and homozygous A allele carriers. The OO genotype was associated with lower levels compared to all other genotypes, which confirm previous findings and is in line with the results for the thromboembolic event. Plasma levels of TM was also found to be associated with ABO genotypes. In contrast to vWF, TM - a membrane protein, expressed on the surface of endothelial cells actively oppose coagulation by inhibiting thrombin. It also indirectly oppose coagulation by the activation of potent coagulation factor inhibitors. Surprisingly, all non-O blood groups except for AO are associated with higher levels of thrombomodulin. In terms of the A genotype, homozygous AA is associated with higher levels of TM compared to heterozygous AO. As the non-O genotypes are associated with higher risk of hypercoagulation-dependent vascular disease, at least partially due to higher levels of coagulation factors such as factor VIII and vWF, one would expect the opposite direction of association for thrombomodulin. However, as the direction of effect (causal direction) is not given by association, there is a possibility that thrombomodulin is expressed in higher levels as a response to increased plasma levels of coagulation factor mediation and activating coagulation. Nevertheless, our results support a previous finding by Blann et al., who found an association between the B blood group and increased levels of soluble TM. They proposed, that the association might be due to that the B antigen positively regulates the expression of TM. However, they also highlighted that the B antigen could be associated with a higher rate of cleavage of TM from the cell surface of the endothelial cells resulting in higher soluble TM levels. This agrees with observations of that during endothelial injury and dysfunction (for example during vascular disease), the expression of TM is reduced leading to an elevated soluble TM release.

4.2 | ABO and inflammatory diseases

We included 17 common inflammatory diseases in this study, selected based on sample size rather than previous association results, but several of the diseases have previously been suggested to be associated with ABO, with the aim of trying to unravel previous ambiguous associations. Surprisingly, ABO was only associated with T1D in our study. There have been some conflicting results in previous literature regarding the possible association between ABO and inflammatory diseases. The associations to allergic diseases were recently reviewed by Dahalan et al. Of the studies that met their criteria, three studies reported a correlation of blood group O to allergic rhinitis, four studies a correlation between blood group O and asthma, one with A and asthma and three a correlation between A and B and atopic dermatitis. Additionally, three studies found no correlation. Little research has been performed on ABO in relation to rheumatic diseases and the few who have, did not yield any strong results. There have been indications of a correlation with ABO and IBDs, including Crohn’s disease, however most correlations seem to be mediated through FUT2, which is the enzyme that determines the secretor status of ABO. A normally functioning enzyme gives rise to the secretor phenotype, where ABO antigens are expressed on endothelial surfaces in the gut. Given the conflicting previous results, it might be that there is no true correlation between variation at the ABO locus directly, rather it being mediated by something else.

4.3 | ABO and type 1 diabetes

We observed a highly increased risk for T1D among individuals homozygous for the B allele, which is a novel finding. The BB genotype is rare, with a frequency of 0.4% in UKB, and this effect has therefore most likely not been captured in previous GWAS for T1D. There have, however, been indications of an association between the ABO secretor status previously. Smyth et al. found an association between a SNP in FUT2 and T1D in European populations, and Ihara et al. found an association between the non-secretor phenotype and susceptibility to T1D. However, in the same study, they did not find an association between the ABO blood groups and T1D. Most previous work point toward the direction of the association being with how and where the ABO antigens are presented and expressed, rather than the genotype itself. Why the homozygous BB genotype show an association with a higher risk of T1D in our study, is therefore still unclear. There is only one previously published association where
blood group B (and O) gave rise to significantly higher intestinal alkaline phosphatase in patients with T1D compared to controls, however the sample size was very small (83 cases and 44 controls) and has to our knowledge not been replicated.51

### 4.4 Novel protein associations

Of the 39 plasma proteins that we found to be associated to variation at the ABO locus, as many as 23 have never been associated to ABO before. Many of the novel proteins (ITGAV, ITGB5, IGFR-B7, EPHB4, PODXL, JAM-B) have functions related to cell adhesion. Also, ITGAV, ITGB5, and IGFR-B7 show similar association patterns, where the A genotypes result in higher protein levels compared to O and B genotypes, whereas EPHB4 and PODXL show similar patterns, where the A genotypes result in significantly lower protein levels compared to the B and O genotypes. One subset (CA9, Gal-9, KLK6, TR-AP, TNFRSF19, TGFR-2) consists of proteins with functions related to tumorogenesis or that have been associated with cancer before. Lastly, many proteins (IFN-gamma-R1, IL-18BP, MARCO, CCL16, AXL, CCL17, XCL1, IL-20) have pro-inflammatory or anti-inflammatory function, antimicrobial functions, or are related to the immune system in other similar ways. The majority (n = 16) of the proteins with novel associations have previously been associated to cancer development, tumorogenesis, or similar. In general, overexpression of these proteins leads to an abnormal cell proliferation or cell growth. One exception is Flt3L, that promotes dendritic cell development. A study by Lai et al.52 used armored T cells engineered to secrete Flt3L and observed a dose-dependent effect on antitumor responses. They hypothesized that the intratumoral Flt3L is critical for driving T cell-mediated inhibition of tumor growth. They further observed that Flt3L-secreting T cells elicited enhanced inhibition of tumor growth. In our study, the ABO B genotypes (AB, BB, and BO) was associated with higher levels of Flt3L compared to both to AA, AO and OO. This might be an indication of individuals with blood group B thus having a lower risk of excessive tumor growth.

### 4.5 Plasma protein association patterns and previous associations

It is important to consider that the proteins measured are soluble proteins measured in plasma, and the levels and associations to the ABO genotypes might differ in the tissue where the proteins are expressed. It is well established that the correlation between mRNA and protein expression within a tissue often is very weak, but less is known about protein expression correlations across tissues.53 In a recent study, with samples from the Human Protein Atlas, Wang et al.53 corroborated that there exist strong differences between both mRNA and protein quantities within and across tissues. However, to what extent the protein expression in different tissues reflect the soluble protein levels still remain uncertain for most proteins.

For many of our investigated proteins, the plasma levels ranged from lower to higher along the pattern of A < O < B or B < O < A which differs from other proteins of either O < A < B or O < B < A, and many disease associations, where the risk is increased/decreased for both A and B compared to O. This pattern was seen both for novel but also for already established associations. One possible explanation for this pattern, could be that A and B antigens differently influence production or elimination rate of a protein, or influence the degree to which a membrane bound protein is cleaved/released into its soluble form.

Several of the previously ABO associated proteins (7 out of 16) have been reported by Emilsson et al.54 They assessed serum proteins and linked co-regulatory protein networks to risk loci for disease. They found that a risk locus for coronary heart disease, rs579459, upstream of ABO was acting both in cis (+/− 150 kb) and in trans on serum protein levels. The variant is defined as a protein single nucleotide polymorphism (pSNP), a variant with allelic imbalance in protein levels. As this variant is associated both to levels of ABO in cis and to several other protein levels in trans, there is a possibility that the changes in levels of the antigen produced gives rise to at least part of the association. As the levels of these seven proteins (CD200, CDH5, ICAM-2, LIF-R, SELE, VEGFR-2, and vWF) were altered by a risk variant for coronary heart disease, this strengthens the proposition that ABO might influence disease risk through changes in protein levels.

### 5 CONCLUSIONS

In this study, we have shown that variation at the ABO locus is associated with common disease risk and the levels of plasma proteins. We have confirmed previous associations as well as tried to disentangle previous findings with low support. By analyzing ABO genotypes rather than blood group phenotypes, we have been able to show differences also at genotype level. We further found an association with the ABO B genotypes and T1D that has not been captured in previous genetic studies. However, as only two groups of diseases were included, namely cardiovascular and inflammatory disease, there is still a gap in assessing the associations to diseases such as infection and cancer, as these also have shown previous association to the ABO blood grouping system. In addition, one of the largest uncertainties is that without tissue measurements in the same cohort, there is no way of establishing the degree of correlation between plasma protein levels and tissue expression levels. The measurements in NSPHS have furthermore also been sampled once, and are thus only from one single point in time. Although one expects a correlation between plasma and tissue levels, especially for biomarkers and putative biomarkers, the degree and direction of correlation is still highly uncertain.

As we did not have access to serologically determined blood groups, nor tissue samples, we were not able to confirm the expressed antigens. Furthermore, we did not investigate Rh-status and secretor status. The ABO blood group status might affect inherent protein
levels, that in turn might influence disease progression or even an individual’s response to medical treatment. Our results clearly show the importance and need to incorporate blood group status, sometimes even subclassifying the standard A, B, and O alleles, in clinical assessment of disease risk and genetic predisposition to disease and medical conditions.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
Julia Höglund and Åsa Johansson designed the study; Julia Höglund and Torgny Karlsson performed the data analysis; Julia Höglund, Torgny Karlsson and Åsa Johansson generated the figures; Julia Höglund, and Åsa Johansson wrote the manuscript; Julia Höglund, Weronica E. Ek, Torgny Karlsson, Therese Johansson and Åsa Johansson interpreted the data, contributed to and reviewed the manuscript.

DATA AVAILABILITY STATEMENT
The data on which this study is based (application number 8260) are available for bona fide researchers from the UKB Resource (http://www.ukbiobank.ac.uk/about-biobank-uk), on filing an application to the UKB. Relevant additional data will be available from the authors on request. For further information, please contact the corresponding author.

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REFERENCES
1. Ohira T, Cushman M, Tsai MY, et al. ABO blood group, other risk factors and incidence of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology (LITE). J Thromb Haemost. 2007;5(7):1455-1461. https://doi.org/10.1111/j.1538-7836.2007.02579.x
2. Teixeira Mello TB, MacHado TFG, Montavão SAL, Ozello MC, Annichino-Bizzacchi JM. Assessing the coagulation factor levels, inherited thrombophilia, and ABO blood group on the risk for venous thrombosis among Brazilians. Clin Appl Thromb Hemost. 2009;15(4): 408-414. https://doi.org/10.1177/1076029607311777
3. Wu O, Bayoumi N, Vickers MA, Clark P. ABO(H) blood groups and vascular disease: a systematic review and meta-analysis. Thromb Haemost. 2008;6:62-69. https://doi.org/10.1111/j.1538-7836.2007.02818.x
4. Wolpin BM, Kabrel C, Varraso R, et al. Prospective study of ABO blood type and the risk of pulmonary embolism in two large cohort studies. Thromb Haemost. 2010;104(5):962-971. https://doi.org/10.1160/TH10-05-0312
5. O’Donnell J, Laffan MA. The relationship between ABO histo-blood group, factor VIII and von Willebrand factor. Transfus Med. 2001;11(4):343-351. https://doi.org/10.1046/j.1365-3148.2001.00315.x
6. Nichols W, Ginsburg D. von Willebrand disease. Medicine (Baltimore). 1997;76:1-20.
7. Kauffmann F, Frette C, Pham Q, Nafissi S, Bertrand J, Oriol R. Associations of blood group-related antigens to FEV1, wheezing, and asthma. Am J Respir Crit Care Med. 1996;153(1):76-82. https://doi.org/10.1164/ajrccm.153.18542166
8. Ronchetti F, Villa MP, Ronchetti R, et al. ABO/secretor genetic complex and susceptibility to asthma in childhood. Eur Respir J. 2001;17(6):1236-1238. https://doi.org/10.1183/09031936.01.99109101
9. Chen YL, Chen JC, Lint TM, et al. ABO/secretor genetic complex is associated with the susceptibility of childhood asthma in Taiwan. Clin Exp Allergy. 2005;35(7):926-932. https://doi.org/10.1111/j.1365-2222.2005.02278.x
10. Falsarella N, Ferreira Al, Nakashima F, Mattos CD, Mattos LC. Evidence of an association between the O blood group and allergic rhinitis. Rev Bras Hematol Hemoter. 2011;33(6):444-448. https://doi.org/10.5581/1516-8484.20110120
11. Toppa N, Narvey VP, Jain AK. The correlation of allergic rhinitis with ABO phenotype. Indian J Otolaryngol Head Neck Surg. 2019;71(s3):1827-1831. https://doi.org/10.1007/s12070-017-1215-1
12. Nnaemeka Alo M. Relationship between ABO and rhesus blood group susceptibility to asthma within Sokoto Metropolis, Nigeria. Int J Immunol. 2015;3(3):37. https://doi.org/10.11648/j.iji.20150303.12
13. Leite ICR, dos Santos Júnior JC, de Sousa CCS, Lima AV, Miranda-Vilela AL. Recognition of phenylthiocarbamide (PTC) in taste test is related to blood group B phenotype, females, and risk of developing food allergy: a cross-sectional Brazilian-based study. Nutr Res. 2018;52:22-38. https://doi.org/10.1016/j.nutres.2017.12.013
14. Brachtel R, Walter H, Beck W, Hille M. Associations between atopic diseases and the polymorphic systems ABO, Kidd, inv and red cell acid phosphatase. Hum Genet. 1979;49(3):337-348. https://doi.org/10.1007/BF00569354
15. Cildag S, Kara Y, Senturk T. ABO blood groups and rheumatic diseases. *Eur J Rheumatol*. 2017;4(4):250-253. https://doi.org/10.5152/eurjrheum.2017.17044

16. Westhoff CM, Shaz BH. Transfusion Medicine and Hemostasis (Second Edition). ABO and H Blood Group System. 2nd ed. Elsevier Inc.; 2013:149–156.

17. Patenaude SI, Seto NOL, Borisova SN, et al. The structural basis for specificity in human abo(h) blood group biosynthesis. *Nat Struct Biol*. 2002;9(9):685-690. https://doi.org/10.1038/nsb832

18. Lang K, Wagner I, Schöne B, et al. ABO allele-level frequency estimation based on population-scale genotyping by next generation sequencing. *BMC Genomics*. 2016;17(1):1-11. https://doi.org/10.1186/s12864-016-2687-1

19. Yip SP. Sequence variation at the human ABO locus. *Ann Hum Genet*. 2002;66(1):1-27. https://doi.org/10.1017/S0003480000008995

20. Yamamoto F, Cid E, Yamamoto M, Blancher A. ABO research in the modern era of genomics. *Transfus Med Rev*. 2012;26(2):103-118. https://doi.org/10.1016/j.transmed.2011.08.002

21. Vlot A, Koppelman S, Bouma B, Simka J. Factor VIII and von Willebrand factor. *Thromb Haemost*. 1989;79:1140-1143.

22. Johansson Å, Alfredsson J, Erikkson N, Wallentin L, Siegbahn A. Genome-wide association study identifies that the ABO blood group system influences interleukin-10 levels and the risk of clinical events in patients with acute coronary syndrome. *PLoS One*. 2015;10(11):1-16. https://doi.org/10.1371/journal.pone.0142518

23. Sun BB, Maranville JC, Peters JE, et al. Genomic atlas of the human plasma proteome. *Nature*. 2018;558(7708):73-79. https://doi.org/10.1038/s41586-018-0175-2

24. Enroth S, Maturi V, Berggrund M, et al. Systemic and specific effects of genetic and lifestyle factors on biomarker variation and use of personally normalized plasma biomarkers for human diseases. *Eur J Rheumatol*. 2017.139(9):1-24. https://doi.org/10.1371/journal.pgen.1007005

25. Ahsan M, Ek WE, Rask-Andersen M, et al. The relative contribution of DNA methylation and genetic variants on protein biomarkers for human diseases. *PLoS Genet*. 2017;13(9):1-24. https://doi.org/10.1371/journal.pgen.1007005

26. Yamamoto F, Clausen H, White T, Marken J, Hakomori SI. Molecular genetic basis of the histo-blood group ABO system. *Nature*. 1990;345(6272):229-233. https://doi.org/10.1038/345229a0

27. Enroth S, Johansson Å, Bosdotter Enroth S, Gyllensten U. Strong effects of genetic and lifestyle factors on biomarker variation and use of personalized cutoffs. *Nat Commun*. 2015;6:4684. https://doi.org/10.1038/ncomms5654

28. Ameur A, Dahlberg J, Olason P, et al. SweGen: a whole-genome data resource of genetic variability in a cross-section of the Swedish population. *Eur J Hum Genet*. 2017;25(11):1253-1260. https://doi.org/10.1038/ejhg.2017.130

29. Li H, Durbin R. Fast and accurate long-read alignment with Burrows-Wheeler transform. *Bioinformatics*. 2010;26(5):589-595. https://doi.org/10.1093/bioinformatics/btp698

30. Van der Auwera GA, Carneiro MO, Hartl C, et al. From FastQ data to Biological interpretation. *Curr Protoc Bioinformatics*. 2013;43(11):110.10.1-11.0.33. https://doi.org/10.1002/9780471250953.1110643

31. Enroth S, Maturi V, Berggrund M, et al. Systemic and specific effects of antihypertensive and lipid-lowering medication on plasma protein biomarkers for cardiovascular diseases. *Sci Rep*. 2018;8(1):1-10. https://doi.org/10.1038/s41598-018-23860-y

32. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2020. https://www.R-project.org/. R package version 1.8.6. 2020. https://CRAN.R-project.org/package=cowplot

33. Augie B. gridExtra: Miscellaneous Functions for “Grid” Graphics. R package version 2.3. 2017. https://CRAN.R-project.org/package=gridExtra

34. Augie B. egg: Extensions for “ggplot2”: Custom Geom, Custom Themes, Plot Alignment, Labelled Panels, Symmetric Scales, and Fixed Panel Size. R package version 0.4.5. 2019. https://CRAN.R-project.org/package=egg

35. Sinnwell JP & Schaid DJ. haplo.stats: Statistical Analysis of Haplotypes with Traits and Covariates when Linkage Phase is Ambiguous. R package version 1.8.6. 2020. https://CRAN.R-project.org/package=haplo.stats

36. World Medical Association General Assembly. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Int Bioethique*. 2004;15(1):124-129. https://doi.org/10.1397/jib.151.0124

37. Groot HE. Sierra LEV, Said MA, Lipiec E, Karper JC, Van Der Harst P. Genetically determined ABO blood group and its associations with health and disease. *Arterioscler Thromb Vasc Biol*. 2020;40:830-838. https://doi.org/10.1161/ATVBAHA.119.313638

38. Giordano NJ, Jansson PS, Young MN, Hagan KA, Kabrhel C. Epidemiology, pathophysiology, stratification, and natural history of pulmonary embolism. *Thoracics Interv Radiol*. 2017;20(3):135-140. https://doi.org/10.1053/j.tvir.2017.07.002

39. Goumidi L, Thibord F, Wiggins KL, et al. Association between ABO haplotypes and the risk of venous thrombosis: impact on disease risk estimation. *Blood*. 2021;137(17):2394-2402. https://doi.org/10.1182/blood.2020008997

40. Blann AD, Daly RJ, Amiral J. The influence of age, gender and ABO blood group on soluble endothelial cell markers and adhesion molecules. *Br J Haematol*. 1996;92(2):498-500. https://doi.org/10.1046/j.1365-2457.1996.0013-1846.x

41. Martin FA, Murphy RP, Cummins PM. Thrombomodulin and the vascular endothelium: insights into functional, regulatory, and therapeutics aspects. *Am J Physiol Heart Circ Physiol*. 2013;304(12):H1585-H1597. https://doi.org/10.1152/ajpheart.00096.2013

42. Demeneuarena M, Devreese K, Vanbelleghem H, et al. Thrombomodulin and endothelial dysfunction: a disease-modifier shared between malignant hypertension and atypical hemolytic uremic syndrome. *Nephron*. 2018;140(1):63-73. https://doi.org/10.1159/000490201

43. Dahalan NH, Tuan Din SA, Mohamad SMB. Association of ABO blood groups with allergic diseases: a scoping review. *BMJ Open*. 2020;10(2):1-8. https://doi.org/10.1136/bmjopen-2019-029559

44. Forni D, Cleynen I, Ferrante M, et al. ABO histo-blood group might modulate predisposition to Crohn’s disease and affect disease behavior. *J Crohns Colitis*. 2014;8(6):489-494. https://doi.org/10.1016/j.jcrob.2013.10.014

45. Smyth DJ, Cooper JD, Howson JMM, et al. FUT2 nonsecretor status links type 1 diabetes susceptibility and atypical hemolytic uremic syndrome. *Diabetes*. 2011;60(11):3081-3084. https://doi.org/10.2337/db11-0638

46. Ihara K, Fukano C, Ayabe T, et al. FUT2 non-secretor status is associated with Type 1 diabetes susceptibility in Japanese children. *Diabet Med*. 2017;34(4):586-589. https://doi.org/10.1111/dme.13288
51. Tibi L, Collier A, Patrick AW, Clarke BF, Smith AF. Plasma alkaline phosphatase isoenzymes in diabetes mellitus. Clin Chim Acta. 1988;177(2):147-155. https://doi.org/10.1016/0009-8981(88)90136-2
52. Lai J, Mardiana S, House IG, et al. Adoptive cellular therapy with T cells expressing the dendritic cell growth factor Flt3L drives epitope spreading and antitumor immunity. Nat Immunol. 2020;21(8):914-926. https://doi.org/10.1038/s41590-020-0676-7
53. Wang D, Eraslan B, Wieland T, et al. A deep proteome and transcriptome abundance atlas of 29 healthy human tissues. Mol Syst Biol. 2019;15(2):1-16. https://doi.org/10.15252/msb.20188503
54. Emilsson V, Ilkov M, Lamb JR, et al. Co-regulatory networks of human serum proteins link genetics to disease. Science. 2018;361(6404):769-773. https://doi.org/10.1126/science.aaq1327

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