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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	For collection of MFI values in proteomics screening and quantification using FlexMap 3D instrument (Luminex® Corp) and the instrument software xPONENT 4.3 was used. For identification of peptides in IC-MS, the search engine Sequest and Proteome Discoverer platform (PD, v1.4.0.339, Thermo Scientific) or MaxQuant (v. 2.1.4.0) . Peaks filter within ProteoWizard provided software tool msConvert (version 3.0.20321-6df943caa). Genotyping by Illumina Infinium Global Screening Array v2.0 and v3.0. Transcriptomics dataset were retrieved from Human Protein Atlas (v18-20) and Genotype-Tissue Expression (GTEx) Project (dbGaP Accession phs000424.v7.p2). Flow cytometry (Cytoflex, Beckman Coulter GmbH, Krefeld, Germany). Thrombinoscope software package (Version 3.0.0.29)
Data analysis	EncyclopeDIA (1.12.31) and Prosit (2018 model),integrated into ProteomicsDB (version 1.1) were employed for MS-DIA data. Eagle v2.4 & Minimac4 for imputation analyses ; Genesis & Plink1.9 and .2 for GWAS analyses; GWAMA (v2.2.2)) and METAL software (no version) for meta-analysis of GWAS results; Imputed genotypes by using MaCH version 1.0.18.c. WGCNA for regulatory gene network analysis. R versions from 3.2.0 to 4.0.5 (R Core Team 2021) for analysis of plasma proteomics and genetic data. GraphPad Prism for figures (version 9.1.2). Flow cytometry, data processed using Cytexpert v.2.5 (Beckman Coulter GmbH, Krefeld, Germany).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

DATA AVAILABILITY:
Source Data are provided with this paper.
The affinity proteomics data for VEBIOS ER generated in this study has been deposited in Figshare, https://doi.org/10.17044/scilifelab.22225942 [125]
The mass spectrometry proteomics data generated in this study has been deposited in the ProteomeXchange Consortium via the PRIDE [126] partner repository with the dataset identifier PXD040913. https://www.ebi.ac.uk/pride/archive/projects/PXD040913
The summary statistic of GWAS data generated in this study is available through GWAS catalogue (GCP ID: GCST90244658). https://www.ebi.ac.uk/gwas/studies/GCST90244658
For legal reasons and to minimize the possibility of unintentionally sharing information that can be used to re-identify private information, participant-level datasets containing full information (e.g. including sex, age, BMI, clinical data) cannot be openly shared. A subset of the data that support the findings of this study are available from the corresponding authors upon reasonable request (e.g. for validation). By contacting the corresponding authors (JO, DAT), procedures for sharing data, analytic methods, and study materials for reproducing the results or replicating the procedure can be arranged. When submitting an access request, please indicate: [name of PI and host organisation/contact details (including your name and email)/scientific purpose of data access request/commitment to inform when the data has been used in a publication/commitment not to host or share the data outside the requesting organisation/statement of non-commercial use of data].
External databases used:
Genotype-Tissue Expression (GTEx) Project (dbGaP Accession phs000424.v7.p2), www.gtexportal.org
Human Protein Atlas, human tissue expression data (v.18-20), www.proteinatlas.org
Homo Sapiens UniProt ID: #UP000009606; www.uniprot.org/proteomes/UP000009606
TOPMed r2 reference panel using Eagle v.2.4 (https://topmedimpute.readthedocs.io/en/latest/getting-started.html)
1000 Genomes phase 3 version reference panel (http://csg.sph.umich.edu/abecasis/mach/download/1000G.Phase3.v5.html
1000 Genomes Total European Ancestry (EUR) population (August 2010 release: http://csg.sph.umich.edu/abecasis/mach/download/1000G-2010-08.html; 1000G.EUR.20100804.tgz).

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	Only data for biological sex has been used in the analyses and reported. All results are adjusted for sex and age. Sex stratified sub-analyses were performed in the different cohorts. Sex was considered in proteomics study design of VEBIOS ER and VEBIOS Coagulation in that cases and controls analysed were matched on sex and age. The sex of the individual anonymous blood donors from which platelets were isolated and used in functional studies was not considered in the analysis.
Population characteristics	VEBIOS ER: 48 cases/48 controls; Age 56.6 (19-89)years/56.6 (23-88) years; female sex 22/22; Smoking 4/9; family history VTE 14/6; Estrogens 5/5. VEBIOS Coagulation: 144 cases/140 controls; Age 51.5(20-70)/53(22-71) years; Female sex 56/55; Smoking 22/19; family history VTE 24/1; Estrogens 26/15; Obesity 90/65. DFW-VTE: 54 cases/146 controls; Age 64.8(20-96)/61.4(18-92); Female sex 23(43%)/90(62%); Estrogens 2/2. FARIVE: 582 cases/576 controls; Age 53.1(17-91)/51.1(18-89); Female sex 348(60%)/330(57%); Smoking 95(16%)/137(24%); Obese 130 (22%)/109(19%); Estrogens 266/249. RETROVE: 308 cases/360 controls); Age 55.4(17-79)/46(20-79); Female sex 142(46%)/183(51%); Obese 86(28%)/45(12.5%). MARTHA: 774 cases; Age 46.7; Female sex 530(68%); Obese 96 (13%)
Recruitment	VEBIOS ER: Patients recruited in ER with suspected VTE. Biased towards patients with symptoms of VTE. Controls biased towards patients with medical ailment/symptoms prompting seeking medical care. This bias does not affect results as the analysis is aimed to finding diagnostic marker apliccable in this overall patient category. No bias between cases and controls as inclusion and blood sampling for biobanking is performed before diagnostic workup identifies cases and controls. VEBIOS ER study is a prospective cohort study carried out at the Emergency Room (ER) at the Karolinska University Hospital in Solna, Sweden, between December 2010 and September 2013. All patients admitted at ER with the suspicion of deep vein thrombosis (DVT) in the lower limbs and/or pulmonary embolism (PE), over 18 years old were eligible for the study.) VEBIOS Coagulation: Patients recruited at outpatient clinic following ending treatment of VTE. Controls sex and age matched controls recruited from population. No apparent bias between cases and controls. VEBIOS Coagulation study is an on-going

case-control study established January 2011 of patients sampled at an outpatient coagulation clinic sampled 1-6 months after discontinuation of 6-12 months anticoagulant treatment after a verified first VTE (DVT to the lower limbs and/or PE), sex and age matched with healthy controls from the population. Patients were between 18 to 70 years of age, free from cancer, severe thrombophilia and pregnancy at inclusion.

DFW-VTE: Patients with suspected VTE recruited in ER. Biased towards patients with symptoms of VTE. Controls biased towards patients with ailment prompting seeking medical care. This bias does not affect results as analysis aimed to finding diagnostic marker in this overall patient category. (The Swedish Karolinska Age Adjusted D-Dimer study (DFW-VTE study) includes patients with clinically suspected acute VTE, prospectively recruited from the ER of Karolinska University Hospital in Huddinge, Stockholm. The patients were out-patients with low-to-high probability of acute PE or DVT in a lower limb.)

FARIVE: Patients recruited during initiation of treatment for VTE, with hospital based recruited controls. Controls biased towards patients with medical ailment resulting in hospital care. (The FARIVE study is a French multicentre case-control study carried out between 2003-2009. The study consists of patients with first confirmed VTE (DVT to the lower limbs and/or PE) from 18 years of age, matched to hospital controls with no previous thrombotic event).

RETROVE: Patients with VTE recruited after ending treatment. Controls recruited from population. No apparent bias. (The Riesgo de Enfermedad TROmboembólica VEnosa (RETROVE) study is a prospective case–control study of 400 consecutive patients with VTE (cancer associated thrombosis excluded) and 400 healthy control volunteers. Individuals were recruited at the Hospital de la Santa Creu i Sant Pau of Barcelona (Spain) between 2012 and 2016. Controls were selected according to the age and sex distribution of the Spanish population (2001 census).

MARTHA: Patients with prior VTE recruited and sampled at single center. No apparent bias. (The Marseille Thrombosis Association study (MARTHA) is a population based single centre study. Recruitment in MARTHA started in 1994 at Timone Hospital in Marseille (France) and is still ongoing. The cohort from 1994 and 2008, includes a total of 1542 VTE-cases (66% women) that donated blood for further analysis. All patients had a history of a first VTE documented by venography, Doppler ultrasound, angiography and/or ventilation/perfusion lung scan).

Ethics oversight

VEBIOS ER and VEBIOS Coagulation: regional research ethics committee in Stockholm, Sweden (KI 2010/636-31/4)
DFW-VTE: regional ethics review board in Stockholm (DNR 2013-2143-31-2).
FARIVE: Paris Broussais-HEGP ethics committee in Paris (2002-034)
RETROVE: Institutional Review Board of the Hospital de la Santa Creu i Sant Pau
MARTHA: Department of Health and Science, France (2008-880 & 09.576)
Platelet experiments: Human Ethics Committee of the Medical University of Vienna (EK237/2004)
HUVEC experiments: Regional Ethics Comitte Stockholm 2015/1552-32

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size

VEBIOS ER: Nested case/control (48 cases/48 controls) derived from cohort of 158 patients with suspected acute VTE. Sample size determined by available number of confirmed cases.
VEBIOS Coagulation: case/control study (144 cases/140 controls). Sample size determined by available number of cases.
DFW-VTE cohort study: 200 patients (54 cases/146 controls). Sample size determined by number of patients included during set study period
FARIVE: Case/control study (582 cases/576 controls). Number determined based on available number of cases with VTE diagnosis.
MARTHA: Case-only cohort derived from case/control study: Size determined by number of patients with previous VTE for which follow-up data was available (669 patients), and for which data for TGP was available (774)
RETROVE:Case/control study (308 cases/360 controls).Sample size determined by number of patients included during set study period.

Data exclusions

Exclusion criteria in patient inclusion described below for respective study.
VEBIOS ER: preestablished exclusion criteria were patients with on-going anticoagulant treatment, pregnancy, active cancer, short life expectancy or lack of capacity to leave approved consent. No data generated from included patients were excluded.
VEBIOS Coagulation: cancer, severe thrombophilia and pregnancy at inclusion. No data from included patients were excluded.
DFW-VTE: No data exclusions.
FARIVE: No data from included patients were excluded.
RETROVE: No data exclusion for the patients in study set.

MARTHA: Patients lacking followup data was excluded from analysis of recurrence. Patients lacking Thrombinoscope data was excluded from analysis of CFHR5 association with TGP.

Replication

The significant association signal for the antibody HPA059937 identified in the in the discovery single binder proteomics screen, identified by LC-MS to be CFHR5, was verified further with 3 different dual binder antibody assays in the discovery case/control set. An association with VTE was validated in the two discovery sets and 3 replication studies using a quantitative dual binder assay. All attempts at replication were successful.
Antibodies used in the quantitative dual binder assay were validated by Western blot and by Immunocapture-mass spectrometry.
Data independent acquisition mass spectrometry (DIA-MS) to perform orthogonal validation of the results obtained from the analysis of CFHR5 plasma levels in VEBIOS ER using the dual binder assay with capture antibody HPA072446, and monoclonal MAB3845.

Randomization

Randomization of samples was performed in the experimental set up using R, where samples were distributed in 96 well plates, balancing the number of case-control samples together with an average of age and sex numbers.

Blinding

We have and internal LIMS systems with new generated sample ID that does not track samples information during the experimental analyses. It was applied to all samples/cohorts analyzed. The origins of individual samples in the experimental set up were not know to the person performing the experiment.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
[ ]	[x] Antibodies
[x]	[ ] Eukaryotic cell lines
[x]	[ ] Palaeontology and archaeology
[x]	[ ] Animals and other organisms
[ ]	[x] Clinical data
[x]	[ ] Dual use research of concern

Methods

n/a	Involved in the study
[x]	[ ] ChIP-seq
[ ]	[x] Flow cytometry
[x]	[ ] MRI-based neuroimaging

Antibodies

Antibodies used

For dual binder validation of HPA059937 target ,anti-human CFHR5 (rabbit polyclonal HPA072446 and HPA073894), mouse anti-human CFHR5 (R&D systems, MAB3845, clone#390513) antibody

For CFHR5 absolute quantification in cohorts, rabbit polyclonal anti-human CFHR5 HPA072446 (Atlas Antibodies, 1,76ug/100ul buffer containing 0.5million magnetic beads) and mouse monoclonal anti-human CFHR5 (R&D systems; MAB3845, clone#390513, 1ug/ml)

For C3 quantification, mouse anti-human C3 and mouse monoclonal anti-human C3 antibodies (Bsi0263, Bsi0190, respectively, Biosystems International) were used in a dual binder assay

For C3c quantification, C3c ELISA kit cat. EKX-JD9XBE-96 (Nordic BioSite, Sweden). Specificity of the assay provided by the company: Vendor statement: This assay has high sensitivity and excellent specificity for detection of C3c. No significant cross-reactivity or interference between C3c and analogues was observed. Note: Limited by current skills and knowledge, it is difficult for us to complete the cross-reactivity detection between C3c and all the analogues, therefore, cross reaction may still exist.

For platelet assays: anti-human CD62P-AF647 (clone#AK4, cat.304918), anti-human CD63-PE (clone#H5C6, cat.353004) or anti-human CD41/CD61-FITC (clone:PAC-1, cat.362804) (all Biolegend)

For proteomics screening: (Table S1, Tab 1. on the main manuscript) - [1,76ug/100ul buffer containing 0.5 million magnetic beads]

HPA Antibody UniProt Protein symbol
HPA059937 Q8IWU6 SULF1
HPA044659 Q08722 CD47
HPA002655 P16109 SELP
HPA003042 P29274 ADORA2A
HPA037423 P30530 AXL
HPA050269 P04196 HRG
HPA001616 P01042 KNG1
HPA046773 Q8TDI8 TMC1
HPA002082 P04275 VWF
HPA026290 P20851 C4BPB

HPA053470 Q30201 HFE
HPA047725 P02763;P19652 ORM1;ORM2
HPA042212 A4FU49 SH3D21
HPA011972 P01127 PDGFB
HPA050724 P15822 HIVEP1
HPA059686 P22352 GPX3
HPA000594 P00451 F8
HPA001815 P04275 VWF
HPA007384 P05160 F13B
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HPA056729 P78423 CX3CL1
HPA064215 Q9UPY5 SLC7A11
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HPA031471 P45844 ABCG1
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HPA068915 P22004 BMP6
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HPA001048 P51813 BMX
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HPA055347 Q8N8G6 C15orf54
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HPA029920 Q8NDD1 C1orf131
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HPA001412 P09919 CSF3
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HPA007328 Q9P2B4 CTTNBP2NL
HPA040361 P78423 CX3CL1
HPA046579 P02778 CXCL10
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HPA048978 P48061 CXCL12
HPA065474 P42830 CXCL5
HPA048879 P80162 CXCL6
HPA045822 P10145 CXCL8
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HPA031991 P25024 CXCR1
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HPA029944 P58658 EVA1C
HPA029945 P58658 EVA1C
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HPA063273 P00742 F10
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HPA058830 P03951 F11
HPA067405 P03951 F11
HPA067557 P03951 F11
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HPA061700 Q9Y624 F11R
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HPA054698 P00734 F2
HPA049045 P25116 F2R
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HPA019328 Q96RI0 F2RL3
HPA031401 Q96RI0 F2RL3
HPA042340 Q96RI0 F2RL3
HPA058724 Q96RI0 F2RL3
HPA049292 P13726 F3
HPA002036 P12259 F5
HPA005942 P12259 F5
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HPA056898 Q6V0I7 FAT4
HPA025287 Q8WUP2 FBLIM1
HPA008928 P06734 FCER2
HPA017162 P06734 FCER2
HPA067430 P06734 FCER2
HPA010718 P12318 FCGR2A
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HPA023128 Q8N895 ZNF366
HPA023526 Q8N895 ZNF366
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HPA055834 Q96IT1 ZNF496

Western blot:
horseradish peroxidase (HRP)-coupled goat anti-rabbit (cat:P0448) or anti-mouse antibodies (cat:P0447)(both, 1:2000, Dako)

Validation

The target of antibody HPA059937 was validated by immunocapture Mass Spectrometry (IC-MS), and results in the discovery single binder proteomics screen was further validated by 3 different dual binder antibody assay, with correlation values >0.7, as descibed in the manuscript.

The HPA072446, targeting the CFHR5 protein, was validated iby 2 dual binder assays and by western blot recognizing correctly the recombinant CFHR5 as described in manuscript. Antibody capture of CFHR5 in plasma was validated by IC-MS.

The monoclonal MAB3845 (R&D) was validated by the vendor (vendor statement: "antibody has been validated for the following applications: Western Blot, Immunoprecipitation") and independently validated in house by IC-MS and Western blot recognizing correctly the recombinant CFHR5, as described in manuscript.

The Dual binder assay for CFHR5 composed of HPA072446 and MAB3845 was validated by correlating with data obtained through Data Independent Aquisition Mass Spectropmetry (DIA-MS) in 96 samples of VEBIOS ER cohort which it is obtained independently of the use of affinity reagents such as antibodies (described in manuscript).

The ELISA kit for C3c was validated by the vendor (Nordic BioSite, cat:EKX-JD9XBE-96). (Vendor statement: "This assay has high sensitivity and excellent specificity for detection of C3c. No significant cross-reactivity or interference between C3c and analogues was observed. Note: Limited by current skills and knowledge, it is difficult for us to complete the cross-reactivity detection between C3c and all the analogues, therefore, cross reaction may still exist").

Validation data for HPA antibodies was obtained from www.proteinatlas.org. (/www.proteinatlas.org/about/antibody+validation)

All antibodies produced internally within the Human Protein Atlas project (HPA antibodies) must pass steps 1-4 in the list below in order to be used for immunohistochemistry and immunocytochemistry/IF. Steps 5-7 provide the basis for evaluating and scoring the antibody reliability. All antibodies that provide a reasonable pattern of immunoreactivity are added to the Human Protein Atlas portal. Feedback from the research community is appreciated and needed for continuous curation of data.

Quality assurance steps for antibodies generated within the Human Protein Atlas project:

The antigen (protein epitope signature tag (PrEST) for a protein is selected as a stretch of 20-150 amino acids with as low identity as possible to proteins from all other putative protein-coding genes, and not including signal peptides or transmembrane regions. Multitarget PrESTs are PrESTs that have more than 80% identity to proteins from more than one gene, and are expected to generate antibodies with multiple targets.

Plasmid inserts are sequenced to assure that the correct PrEST sequence is cloned.

Size of the resulting recombinant protein (including the specific PrEST) is analyzed using mass spectrometry to assure that the correct antigen has been produced and purified.

To control for cross-reactivity, affinity purified antibodies are tested for sensitivity and specificity on protein arrays consisting of glass slides with spotted PrEST fragments.

Antibody specificity is analyzed using Western blot in a standardized setup. Total protein lysates from a limited number of tissues (liver and tonsil), cell lines (RT4 and U-251 MG), and human plasma are used to evaluate the antibody target binding in a Western blot setting. Antibodies with an uncertain standard Western blot are reanalyzed using an over-expression lysate as a positive control.

Immunohistochemical staining of normal and cancer tissue is examined and annotated by specially educated personnel, and the staining patterns are compared with available gene/RNA/protein characterization data.

High resolution confocal microscopy images of human cell lines stained by indirect immunofluorescence are annotated for subcellular localizations by trained cell biologists, and the subcellular localization patterns are compared with the immunohistochemical staining and available experimental protein characterization data.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	N/A
Study protocol	Not a clinical trial. All studies included were observational studies. A discovery proteomics screen was first performed in a nested case/control study (48+48 patients) derived from a cohort of patients with suspected acute VTE, where patients where VTE could be excluded following diagnostic workup served as controls (VEBIOS ER). One target overlapping with a published dataset of proteins associated with prior risk of VTE in a case/control study, with healthy controls derived from the population, (VEBIOS Coagulation), was selected for further study. Target replication was performed in 1) a cohort of patients with suspected acute VTE (DFW-VTE), a case/control study of newly diagnosed patients with VTE, sampled during treatment initiation, using hospital based controls (FARIVE), and a case/control study of patients with prior VTE using population based healthy controls (RETROVE). Testing for assocation of target with recurrent VTE was performed in a case-only sample set of patients with prior VTE followed up to 12 years following the event (MARTHA).
Data collection	VEBIOS ER: Setting and sampling for biobank - Emergency Department of Karolinska University Hospital Solna, Sweden. Recruitment period December 2010 to September 2013 . Data collection from study inclusion questionare together with retrieval from hospital records following discharge. Routine laboratory tests (e.g CRP) was retrieved from hospital data system. Proteomics screen performed in SciLifeLab Plasma Profiling Facility. Biomarker measurements on biobanked samples performed in SciLifeLab research laboratory VEBIOS Coagulation: Setting and sampling for biobank - Coagulation Unit outpatient clinic at the Karolinska University Hospital (Sweden). Recruitment period January 2011 to December 2017. Data collected from questionare at time of inclusion by research nurse. Routine laboratory tests performed at the Hospital Clinical Chemistry laboratory. Biomarker measurements on biobanked samples performed at SciLifeLab research lab DFW-VTE: Setting and sampling for biobank.- Emergency Department at Karolinska University Hospital Huddinge. Recruitment period April 2014 and May 2015. Data collection from hospital records. Routine lab tests performed at Hospital Clinical Chemistry Laboratory on fresh samples. Biomarker measurements on biobanked samples performed at SciLifeLab research lab FARIVE: Setting and sampling for biobank - multicentre case-control study, in patients and outpatients. Recruitment period 2003-2009. Data collection through study questionarie. Biomarker measurements performed in SciLifeLab research lab RETROVE: Setting and sampling for biobank - Hospital de la Santa Creu i Sant Pau of Barcelona (Spain). Recruitment period between 2012 and 2016. MARTHA: Recruitment in Timone Hospital in Marseille (France) and is still ongoing. Patients included in current included between 1994 and 2008. Biomarker measurements at SciLifeLab research lab.
Outcomes	Clinical diagnosis of DVT and/or PE (acute, previous or recurrent VTE)

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Blood was drawn from healthy volunteers free from any anti-platelet therapy for at least 10 days and anticoagulated with sodium citrate or hirudin. All donors signed informed consent, in accordance with approval of the Human Ethics Committee of the Medical University of Vienna (EK237/2004) and the Declaration of Helsinki. Whole blood was centrifuged (120 g, 20 minutes, room temperature) and platelet-rich plasma (PRP) harvested. To obtain isolated platelets, PRP was diluted with PBS and treated with PGI2 (100 ng/ml), centrifuged for 90 sec at 3000 x g and platelets were resuspended in PBS. This step was repeated twice. Platelet-rich plasma (PRP) or isolated platelets were incubated with recombinant CFHR5 (rCFHR5) in PBS (6 µg/ml, 3845-F5, R&D systems) or PBS alone for 10 minutes before treatment with varying concentrations of ADP (1-5 µM), TRAP-6 (3-15 µM) or convluxin (1-6 ng/ml) for 15 minutes. Platelets were subsequently incubated with primary antibodies: anti-human CD62P-AF647 (AK4), anti-human CD63-PE (H5C6) or anti-human CD41/CD61-FITC (PAC-1) (all Biolegend) for 20 minutes, washed (PBS then 500 g for 10 minutes), then fixed with 1 % paraformaldehyde and incubated with Alexa Fluor 647-streptavidin (Jackson Immuno Research, Ely, UK) for 20 minutes. In some experiments PRP was incubated for 20 minutes with 0.25% DMSO, 100µM compstatin, PBS, 10µg/ml anti-C3a/C3a (desArg)(clone K13/16), prior to assay as described above.
Instrument	(Cytoflex, Beckman Coulter GmbH, Krefeld, Germany)

Software	Cytexpert v2.5 (Beckman Coulter GmbH, Krefeld, Germany).
Cell population abundance	The abundance of the platelets were more than 99%, determined by flow cytometry according to their forward and side scatter.
Gating strategy	First, platelets were identified according to their forward (FSC) and side scatter (SSC, x-axis of all blots). More than 99% of the cell population were platelets. Subsequently, expression of different platelet activation markers (CD62P, Pac-1, CD63) were determined.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.