Supplemental Methods

Atherosclerosis Risk in Communities (ARIC)

The ARIC study is a prospective population-based study evaluating atherosclerosis and cardiovascular diseases in 15,792 men and women, including 11,478 non-Hispanic whites and 4,314 African Americans, in 4 U.S. communities (suburban Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina, and Jackson, Mississippi) [1]. Participants were age 45- 64 years at their baseline examination in 1987-1989 when blood was drawn for DNA extraction and coagulation testing [2]. VWF antigen was determined by a commercial ELISA kit (American Bioproducts) and reported as a percentage of the Universal Coagulation Reference Plasma (Thromboscreen, Pacific Hemostasis; Curtin Matheson Scientific Inc) or IU/dL. FVIII activity was measured by the ability of a testing sample to correct the clotting time of human FVIII-deficient plasma and reported as IU/dL (George King Biomedical Inc). The reliability coefficient (1 − intra-individual variance/total variance) obtained from repeat testing of individuals over several weeks was 0.68 for VWF and 0.86 for FVIII. Baseline measures of VWF and FVIII were available on 2,354 AA individuals from the ARIC cohort. Of these, 324 were sequenced as part of ESP and 2,030 were imputed using CARe GWAS data.

Coronary Artery Risk Development in Young Adults (CARDIA)

The CARDIA study is a prospective, multi-center investigation of the natural history and etiology of cardiovascular disease in African Americans and whites 18-30 years of age at the time of initial examination [3,4]. Participants were recruited at random during 1985-86 primarily from geographically based populations in Birmingham AL, Chicago IL, and Minneapolis MN and, in Oakland, CA, from the membership of the Kaiser-Permanente Health Plan. The initial examination included 5,115 participants selectively recruited to represent proportionate racial, gender, age, and education groups from each of the four communities. Seven follow-up examinations have been conducted at years 2, 5, 7, 10, 15, 20, and 25. The blood collection and processing was virtually identical to that of the ARIC study. DNA extraction for genetic studies was performed at the year 10 examination. VWF and FVIII testing were performed in 698

AA at year 5, and ristocetin cofactor activity was measured in 324 AA at Year 7 [21]. FVIII coagulant activity was assayed by a one-stage system with reagents from Pacific Hemostasis and George King Biomedical, Inc. VWF antigen was measured by ELISA (American Bioproducts Co). VWF activity was measured using the ristocetin cofactor assay. VWF antigen or FVIII coagulant activity were available on 353 AA individuals from CARDIA for the current analysis. Of these, 40 were sequenced as part of ESP and 313 were imputed using CARe GWAS data.

Multi-Ethnic Study of Atherosclerosis (MESA)

The MESA is evaluating preclinical atherosclerosis and its progression in 4 racial/ethnic groups. Details of the design have been published [5]. Briefly, 6814 men and women age 45-84 years whose self-reported race/ethnicity was white, black, Chinese, or Hispanic were recruited from six US communities: Baltimore City and Baltimore County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan and the Bronx, NY; and St. Paul, MN. All participants were free of clinical diagnoses of CVD. Laboratory assays were performed at the University of Vermont (Burlington, VT) [6]. Factor VIII coagulant activity was measured at baseline in all MESA participants using the Sta-R analyzer (STA-Deficient VIII; Diagnostica Stago, Parsippany, NJ, USA) (CV=10%). VWF antigen was measured at baseline in a random sample of 1000 individuals chosen from the first 5030 enrolled participants using immunoturbidometric methods on the Sta-R analyzer (Liatest VWF; Diagnostica Stago, Parsippany, NJ, USA). Data on FVIII were available for 1,607 AA individuals and on VWF for 193 individuals. Of these, 151 were sequenced as part of ESP and 1456 were imputed using CARe GWAS data.

Women's Health Initiative (WHI)

The WHI clinical trial of conjugated equine estrogen with our without medroxyprogesterone acetate, compared to placebo included 27,347 postmenopausal women aged 50 to 79 years at 40 US centers [7]. Factor VIII activity and VWF antigen were measured at the baseline WHI exam in the same lab with the same methods as in MESA. We included 153 AA women (132 with VWF antigen and 154 with factor VIII activity) from the clinical trial of hormone therapy who had consented to genetic research and who were sampled as part of a case-control study of laboratory risk factors for MI, stroke and venous thrombosis [8,9]. Of these, 80 were sequenced as part of ESP and 74 were imputed using SHARe GWAS data.

Meta-analysis of cohort-specific results and tests of homogeneity

All analyses were performed separately within each cohort (for those with imputed genotype data) and separately for those with sequence data. Study-level regression results were then combined using inverse-variance weighted fixed-effects meta-analysis to derive an overall *P*-value and effect estimate (β coefficients and standard error) for each single nucleotide variant [10]. We tested for consistency of results between studies by using Cochran's Q statistic and the I^2 inconsistency metric [11]. The I^2 metric ranges from 0-100%, and measures the degree of inconsistency across studies in a meta-analysis as the percentage of total variation across studies that is due to heterogeneity rather than chance. Low, moderate, and high degrees of heterogeneity between studies is defined as I^2 values of 25%, 50%, and 75%, respectively.

In silico **prediction of** ***VWF*** **missense variants as functionally deleterious vs. neutral**

We characterized the potential impact of each *VWF* missense variant on VWF structure/function using the algorithm Condel (CONsensus DELeteriousness score of non-synonymous single nucleotide variants) [10]. Condel integrates the output of three widely used *in silico* approaches that assess the impact of non-synonymous SNVs on protein function: SIFT [11], Polyphen2 [12] and MutationAssessor [13]. A combination of multiple algorithms can improve prediction accuracy of classifying mutations as deleterious or neutral [10]. SIFT and MutationAssessor are based on evolutionary conservation of amino acids in a particular protein family, while Polyphen2 compares various protein structural- and sequence-based features between a wild-type and mutant. In the consensus prediction made by Condel, the probability that a predicted deleterious mutation is not a false positive and the probability that a predicted neutral mutation is not a false negative are employed as weights. As an additional method to predict the functional consequences of a VWF missense variant, we used a DNA sequence conservation-based method called Genomic Evolutionary Rate Profiling (GERP) [14], which identifies functionally constrained DNA sequence elements using multiple sequence alignments to quantify nucleotide substitution deficits ("rejected substitutions") that reflect the strength of past purifying selection.

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NHLBI GO Exome Sequencing Project
BroadGO

Stacey B. Gabriel (Broad Institute)[4, 5, 11, 16, 17], David M. Altshuler (Broad Institute, Harvard Medical School, Massachusetts General Hospital)[1, 5, 7, 17], Gonçalo R. Abecasis (University of Michigan)[3, 5, 9, 13, 15, 17], Hooman Allayee (University of Southern California)[5], Sharon Cresci (Washington University School of Medicine)[5], Mark J. Daly (Broad Institute, Massachusetts General Hospital), Paul I. W. de Bakker (Broad Institute, Harvard Medical School, University Medical Center Utrecht)[3, 15], Mark A. DePristo (Broad Institute)[4, 13, 15, 16], Ron Do (Broad Institute)[5, 9, 13, 15], Peter Donnelly (University of Oxford)[5], Deborah N. Farlow (Broad Institute)[3, 4, 5, 12, 14, 16, 17], Tim Fennell (Broad Institute), Kiran Garimella (University of Oxford)[4, 16], Stanley L. Hazen (Cleveland Clinic)[5], Youna Hu (University of Michigan)[3, 9, 15], Daniel M. Jordan (Harvard Medical School, Harvard University)[13], Goo Jun (University of Michigan)[13], Sekar Kathiresan (Broad Institute, Harvard Medical School, Massachusetts General Hospital)[5, 8, 9, 12, 14, 15, 17, 20], Hyun Min Kang (University of Michigan)[9, 13, 16], Adam Kiezun (Broad Institute)[5, 13, 15], Guillaume Lettre (Broad Institute, Montreal Heart Institute, Université de Montréal)[1, 2, 13, 15], Bingshan Li (University of Michigan)[3], Mingyao Li (University of Pennsylvania)[5], Christopher H. Newton-Cheh (Broad Institute, Massachusetts General Hospital, Harvard Medical School)[3, 8, 15], Sandosh Padmanabhan (University of Glasgow School of Medicine)[3, 12, 15], Gina Peloso (Broad Institute, Harvard Medical School, Massachusetts General Hospital)[5], Sara Pulit (Broad Institute)[3, 15], Daniel J. Rader (University of Pennsylvania)[5], David Reich (Broad Institute, Harvard Medical School)[15], Muredach P. Reilly (University of Pennsylvania)[5], Manuel A. Rivas (Broad Institute, Massachusetts General Hospital)[5], Steve Schwartz (Fred Hutchinson Cancer Research Center)[5, 12], Laura Scott (University of Michigan)[1], David S. Siscovick (University of Washington)[5, 1, 25], John A. Spertus (University of Missouri Kansas City)[5], Nathan O. Stitziel (Brigham and Women's Hospital)[5, 15], Nina Stoletzki (Brigham and Women's Hospital, Broad Institute, Harvard Medical School)[13], Shamil R. Sunyaev (Brigham and Women's Hospital, Broad Institute, Harvard Medical School)[1, 3, 5, 13, 15], Benjamin F. Voight (Broad Institute, Massachusetts General Hospital), Cristen J. Willer (University of Michigan)[1, 9, 13, 15]

HeartGO

Stephen S. Rich (University of Virginia)[2, 4, 7, 8, 9, 11,14, 15, 17, 18, 31], Ermeg Akylbekova (Jackson State University, University of Mississippi Medical Center)[29], Larry D. Atwood* (Boston University)[1, 11, 28], Christie M. Ballantyne (Baylor College of Medicine, Methodist DeBakey Heart Center)[9, 22], Maja Barbalic (University of Texas Health Science Center Houston)[9, 14, 15, 17, 22], R. Graham Barr (Columbia University Medical Center)[10, 31], Emelia J. Benjamin (Boston University)[14, 20, 28], Joshua Bis (University of Washington)[15, 23], Eric Boerwinkle (University of Texas Health Science Center Houston)[3, 5, 9, 13, 15, 17, 22], Donald W. Bowden (Wake Forest University)[1, 31], Jennifer Brody (University of Washington)[3, 5, 15, 23], Matthew Budoff (Harbor-UCLA Medical Center)[31], Greg Burke (Wake Forest University)[5, 31], Sarah Buxbaum (Jackson State University)[3, 13, 15, 29], Jeff Carr (Wake Forest University)[25, 29, 31], Donna T. Chen (University of Virginia)[6, 11], Ida Y. Chen (Cedars-Sinai Medical Center)[1, 31], Wei-Min Chen (University of Virginia)[13, 15, 18], Pat Concannon (University of Virginia)[11], Jacy Crosby (University of Texas Health Science Center Houston)[22], L. Adrienne Cupples (Boston University)[1, 3, 5, 9, 13, 15, 18, 28], Ralph D'Agostino (Boston University)[28], Anita L. DeStefano (Boston University)[13, 18], [28], Albert Dreisbach (University of Mississippi Medical Center)[3, 29], Josée Dupuis (Boston University)[1, 28], J. Peter Durda (University of Vermont)[15, 23], Jaclyn Ellis (University of North Carolina Chapel Hill)[1], Aaron R. Folsom (University of Minnesota)[5], [22], Myriam Fornage (University of Texas Health Science Center Houston)[3, 18, 25], Caroline S. Fox (National Heart, Lung, and Blood Institute)[1, 28], Ervin Fox (University of Mississippi Medical Center)[3, 9, 29], Vincent Funari (Cedars-Sinai Medical Center)[1, 11, 31], Santhi K. Ganesh (University of Michigan)[2, 22], Julius Gardin (Hackensack University Medical Center)[25], David Goff (Wake Forest University)[25], Ora Gordon (Cedars-Sinai Medical Center)[11, 31], Wayne Grody (University of California Los Angeles)[11, 31], Myron Gross (University of Minnesota)[1, 5, 14, 25], Xiuqing Guo (Cedars-Sinai Medical Center)[3, 15, 31], Ira M. Hall (University of Virginia), Nancy L. Heard-Costa (Boston University)[1, 11, 28], Susan R. Heckbert (University of Washington)[10, 14, 20, 23], Nicholas Heintz (University of Vermont), David M. Herrington (Wake Forest University)[5, 31], DeMarc Hickson (Jackson State University, University of Mississippi Medical Center)[29], Jie Huang (National Heart, Lung, and Blood Institute)[5, 28], Shih-Jen Hwang (Boston University, National Heart, Lung, and Blood Institute)[3, 28], David R. Jacobs (University of Minnesota)[25], Nancy S. Jenny (University of Vermont)[1, 2, 23], Andrew D. Johnson (National Heart, Lung, and Blood Institute)[2, 5, 11, 28], Craig W. Johnson (University of Washington)[15, 31], Steven Kawut (University of Pennsylvania)[10,31], Richard Kronmal (University of Washington)[31], Raluca Kurz (Cedars-Sinai Medical Center)[11, 31], Ethan M. Lange (University of North Carolina Chapel Hill)[3, 5, 9, 13, 34], Leslie A. Lange (University of North Carolina Chapel Hill)[1, 2, 3, 5, 9, 12, 13, 15, 17, 18, 20, 25, 34], Martin G. Larson (Boston University)[3, 15, 28], Mark Lawson (University of Virginia), Cora E. Lewis (University of Alabama at Birmingham)[25,34], Daniel Levy (National Heart, Lung, and Blood Institute)[3, 15, 17, 28], Dalin Li (Cedars-Sinai Medical Center)[11, 15, 31], Honghuang Lin (Boston University)[20, 28], Chunyu Liu (National Heart, Lung, and Blood Institute)[3, 28], Jiankang Liu (University of Mississippi Medical Center)[1, 29], Kiang Liu (Northwestern University)[25], Xiaoming Liu (University of Texas Health Science Center Houston)[15, 22], Yongmei Liu (Wake Forest University)[2, 5, 31], William T. Longstreth (University of Washington)[18, 23], Cay Loria (National Heart, Lung, and Blood Institute)[25], Thomas Lumley (University of Auckland)[9, 23], Kathryn Lunetta (Boston University)[28], Aaron J. Mackey (University of Virginia)[16, 18], Rachel Mackey (University of Pittsburgh)[1, 23, 31], Ani Manichaikul (University of Virginia)[8, 15, 18, 31], Taylor Maxwell (University of Texas Health Science Center Houston)[22], Barbara McKnight (University of Washington)[15, 23], James B. Meigs (Brigham and Women's Hospital, Harvard Medical School, Massachusetts General Hospital)[1, 28], Alanna C. Morrison (University of Texas Health Science Center Houston)[3, 15, 17], Solomon K. Musani (University of Mississippi Medical Center)[3, 29], Josyf C. Mychaleckyj (University of Virginia)[13, 15, 31], Jennifer A. Nettleton (University of Texas Health Science Center Houston)[9, 22], Kari North (University of North Carolina Chapel Hill)[1, 3, 9, 10, 13, 15, 17, 34], Christopher J. O'Donnell (Massachusetts General Hospital, National Heart, Lung, and Blood Institute)[2, 5, 9, 11, 12, 14, 15, 17, 20, 28], Daniel O'Leary (Tufts University School of Medicine)[25, 31], Frank S. Ong (Cedars-Sinai Medical Center)[3, 11, 31], Walter Palmas (Columbia University)[3, 15, 31], James S. Pankow (University of Minnesota)[1, 22], Nathan D. Pankratz (Indiana University School of Medicine)[15, 25], Shom Paul (University of Virginia), Marco Perez (Stanford University School of Medicine), Sharina D. Person (University of Alabama at Birmingham, University of Alabama at Tuscaloosa)[25], Joseph Polak (Tufts University School of Medicine)[31], Wendy S. Post (Johns Hopkins University)[3, 9, 11, 14, 20, 31], Bruce M. Psaty (Group Health Research Institute, University of Washington)[3, 5, 9, 11, 14, 15, 23], Aaron R. Quinlan (University of Virginia)[18, 19], Leslie J. Raffel (Cedars-Sinai Medical Center)[6, 11, 31], Vasan S. Ramachandran (Boston University)[3, 28], Alexander P. Reiner (Fred Hutchinson Cancer Research Center, University of Washington)[1, 2, 3, 5, 9, 11, 12, 13, 14, 15, 20, 25, 34], Kenneth Rice (University of Washington)[15, 23], Jerome I. Rotter (Cedars-Sinai Medical Center)[1, 3, 6, 8, 11, 15, 31], Jill P. Sanders (University of Vermont)[23], Pamela Schreiner (University of Minnesota)[25], Sudha Seshadri (Boston University)[18, 28], Steve Shea (Brigham and Women's Hospital, Harvard University)[28], Stephen Sidney (Kaiser Permanente Division of Research, Oakland, CA)[25], Kevin Silverstein (University of Minnesota)[25], David S. Siscovick (University of Washington)[5, 1, 25], Nicholas L. Smith (University of Washington)[2, 15, 20, 23], Nona Sotoodehnia (University of Washington)[3, 15, 23], Asoke Srinivasan (Tougaloo College)[29], Herman A. Taylor (Jackson State University, Tougaloo College, University of Mississippi Medical Center)[5, 29], Kent Taylor (Cedars-Sinai Medical Center)[31], Fridtjof Thomas (University of Texas Health Science Center Houston)[3, 22], Russell P. Tracy (University of Vermont)[5, 9, 11, 12, 14, 15, 17, 20, 23], Michael Y. Tsai (University of Minnesota)[9, 31], Kelly A. Volcik (University of Texas Health Science Center Houston)[22], Chrstina L Wassel (University of California San Diego)[9, 15, 31], Karol Watson (University of California Los Angeles)[31], Gina Wei (National Heart, Lung, and Blood Institute)[25], Wendy White (Tougaloo College)[29], Kerri L. Wiggins (University of Vermont)[23], Jemma B. Wilk (Boston University)[10, 28], O. Dale Williams (Florida International University)[25], Gregory Wilson (Jackson State University)[29], James G. Wilson (University of Mississippi Medical Center)[1, 2, 5, 8, 9, 11, 12, 14, 17, 20, 29], Phillip Wolf (Boston University)[28], Neil A. Zakai (University of Vermont)[2, 23]

ISGS and SWISS
John Hardy (Reta Lila Weston Research Laboratories, Institute of Neurology, University College London)[18], James F. Meschia (Mayo Clinic)[18], Michael Nalls (National Institute on Aging)[2, 18], Stephen S. Rich (University of Virginia)[2, 4, 7, 8, 9, 11, 14, 15, 17, 18, 31], Andrew Singleton (National Institute on Aging)[18], Brad Worrall (University of Virginia)[18]

LungGO
Michael J. Bamshad (Seattle Children's Hospital, University of Washington)[4, 6, 7, 8, 10, 11, 13, 15, 17, 27], Kathleen C. Barnes (Johns Hopkins University)[2, 10, 12, 14, 15, 17, 20, 24, 30, 32], Ibrahim Abdulhamid (Children's Hospital of Michigan)[27], Frank Accurso (University of Colorado)[27], Ran Anbar (Upstate Medical University)[27], Terri Beaty (Johns Hopkins University)[24, 30], Abigail Bigham (University of Washington)[13, 15, 27], Phillip Black (Children's Mercy Hospital)[27], Eugene Bleecker (Wake Forest University)[33], Kati Buckingham (University of Washington)[27], Anne Marie Cairns (Maine Medical Center)[27], Wei-Min Chen (University of Virginia)[13, 15, 18], Daniel Caplan (Emory University)[27], Barbara Chatfield (University of Utah)[27], Aaron Chidekel (A.I. Dupont Institute Medical Center)[27], Michael Cho (Brigham and Women's Hospital, Harvard Medical School)[13, 15, 24], David C. Christiani (Massachusetts General Hospital)[21], James D. Crapo (National Jewish Health)[24, 30], Julia Crouch (Seattle Children's Hospital)6, Denise Daley (University of British Columbia)[30], Anthony Dang (University of North Carolina Chapel Hill)[26], Hong Dang (University of North Carolina Chapel Hill)[26], Alicia De Paula (Ochsner Health System)[27], Joan DeCelie-Germana (Schneider Children's Hospital)[27], Allen Dozor (New York Medical College, Westchester Medical Center)[27], Mitch Drumm (University of North Carolina Chapel Hill)[26], Maynard Dyson (Cook Children's Med. Center)[27], Julia Emerson (Seattle Children's Hospital, University of Washington)[27], Mary J. Emond (University of Washington)[10, 13, 15, 17, 27], Thomas Ferkol (St. Louis Children's Hospital, Washington University School of Medicine)[27], Robert Fink (Children's Medical Center of Dayton)[27], Cassandra Foster (Johns Hopkins University)[30], Deborah Froh (University of Virginia)[27], Li Gao (Johns Hopkins University)[24, 30, 32], William Gershan (Children's Hospital of Wisconsin)[27], Ronald L. Gibson (Seattle Children's Hospital, University of Washington)[10, 27], Elizabeth Godwin (University of North Carolina Chapel Hill)[26], Magdalen Gondor (All Children's Hospital Cystic Fibrosis Center)[27], Hector Gutierrez (University of Alabama at Birmingham)[27], Nadia N. Hansel (Johns Hopkins University, Johns Hopkins University School of Public Health)[10, 15, 30], Paul M. Hassoun (Johns Hopkins University)[10, 14, 32], Peter Hiatt (Texas Children's Hospital)[27], John E. Hokanson (University of Colorado)[24], Michelle Howenstine (Indiana University, Riley Hospital for Children)[27], Laura K. Hummer (Johns Hopkins University)[32], Seema M. Jamal (University of Washington)[11], Jamshed Kanga (University of Kentucky)[27], Yoonhee Kim (National Human Genome Research Institute)[24, 32], Michael R. Knowles (University of North Carolina Chapel Hill)[10, 26], Michael Konstan (Rainbow Babies & Children's Hospital)[27], Thomas Lahiri (Vermont Children's Hospital at Fletcher Allen Health Care)[27], Nan Laird (Harvard School of Public Health)[24], Christoph Lange (Harvard School of Public Health)[24], Lin Lin (Harvard Medical School)[21], Xihong Lin (Harvard School of Public Health)[21], Tin L. Louie (University of Washington)[13, 15, 27], David Lynch (National Jewish Health)[24], Barry Make (National Jewish Health)[24], Thomas R. Martin (University of Washington, VA Puget Sound Medical Center)[10, 21], Steve C. Mathai (Johns Hopkins University)[32], Rasika A. Mathias (Johns Hopkins University)[10, 13, 15, 30, 32], John McNamara (Children's Hospitals and Clinics of Minnesota)[27], Sharon McNamara (Seattle Children's Hospital)[27], Deborah Meyers (Wake Forest University)[33], Susan Millard (DeVos Children's Butterworth Hospital, Spectrum

Health Systems)[27], Peter Mogayzel (Johns Hopkins University)[27], Richard Moss (Stanford University)[27], Tanda Murray (Johns Hopkins University)[30], Dennis Nielson (University of California at San Francisco)[27], Blakeslee Noyes (Cardinal Glennon Children's Hospital)[27], Wanda O'Neal (University of North Carolina Chapel Hill)[26], David Orenstein (Children's Hospital of Pittsburgh)[27], Brian O'Sullivan (University of Massachusetts Memorial Health Care)[27], Rhonda Pace (University of North Carolina Chapel Hill)[26], Peter Pare (St. Paul's Hospital)[30], H. Worth Parker (Dartmouth-Hitchcock Medical Center, New Hampshire Cystic Fibrosis Center)[27], Mary Ann Passero (Rhode Island Hospital)[27], Elizabeth Perkett (Vanderbilt University)[27], Adrienne Prestridge (Children's Memorial Hospital)[27], Nicholas M. Rafaels (Johns Hopkins University)[30], Bonnie Ramsey (Seattle Children's Hospital, University of Washington)[27], Elizabeth Regan (National Jewish Health)[24], Clement Ren (University of Rochester)[27], George Retsch-Bogart (University of North Carolina Chapel Hill)[27], Michael Rock (University of Wisconsin Hospital and Clinics)[27], Antony Rosen (Johns Hopkins University)[32], Margaret Rosenfeld (Seattle Children's Hospital, University of Washington)[27], Ingo Ruczinski (Johns Hopkins University School of Public Health)[13, 15, 30], Andrew Sanford (University of British Columbia)[30], David Schaeffer (Nemours Children's Clinic)[27], Cindy Sell (University of North Carolina Chapel Hill)[26], Daniel Sheehan (Children's Hospital of Buffalo)[27], Edwin K. Silverman (Brigham and Women's Hospital, Harvard Medical School)[24, 30], Don Sin (Children's Medical Center of Dayton)[30], Terry Spencer (Elliot Health System)[27], Jackie Stonebraker (University of North Carolina Chapel Hill)[26], Holly K. Tabor (Seattle Children's Hospital, University of Washington)[6, 10, 11, 17, 27], Laurie Varlotta (St. Christopher's Hospital for Children)[27], Candelaria I. Vergara (Johns Hopkins University)[30], Robert Weiss [30], Fred Wigley (Johns Hopkins University)[32], Robert A. Wise (Johns Hopkins University)[30], Fred A. Wright (University of North Carolina Chapel Hill)[26], Mark M. Wurfel (University of Washington)[10, 14, 21], Robert Zanni (Monmouth Medical Center)[27], Fei Zou (University of North Carolina Chapel Hill)[26]

SeattleGO

Deborah A. Nickerson (University of Washington)[3, 4, 5, 7, 8, 9, 11, 15, 17, 18, 19], Mark J. Rieder (University of Washington)[4, 11, 13, 15, 16, 17, 19], Phil Green (University of Washington), Jay Shendure (University of Washington)[1, 8, 14, 16, 17], Joshua M. Akey (University of Washington)[13, 14, 15], Michael J. Bamshad (Seattle Children's Hospital, University of Washington)[4, 6, 7, 8, 10, 11, 13, 15, 17, 27], Carlos D. Bustamante (Stanford University School of Medicine)[3, 13, 15], David R. Crosslin (University of Washington)[2, 9], Evan E. Eichler (University of Washington)[19], P. Keolu Fox[2], Wenqing Fu (University of Washington)[13], Adam Gordon (University of Washington)[11], Simon Gravel (Stanford University School of Medicine)[13, 15], Gail P. Jarvik (University of Washington)[9, 15], Jill M. Johnsen (Puget Sound Blood Center, University of Washington)[2], Mengyuan Kan (Baylor College of Medicine)[13], Eimear E. Kenny (Stanford University School of Medicine)[3, 13, 15], Jeffrey M. Kidd (Stanford University School of Medicine)[13, 15], Fremiet Lara-Garduno (Baylor College of Medicine)[15], Suzanne M. Leal (Baylor College of Medicine)[1, 13, 15, 16, 17, 19, 20], Dajiang J. Liu (Baylor College of Medicine)[13, 15], Sean McGee (University of Washington)[13, 15, 19], Timothy D. O'Connor (University of Washington)[13], Bryan Paeper (University of Washington)[16], Peggy D. Robertson (University of Washington)[4], Joshua D. Smith (University of Washington)[4, 16, 19], Jeffrey C. Staples (University of Washington), Jacob A. Tennessen (University of Washington)[13], Emily H. Turner (University of Washington)[4, 16], Gao Wang (Baylor College of Medicine)[1,13,20], Qian Yi (University of Washington)[4]

WHISP

Rebecca Jackson (Ohio State University)[1, 2, 4, 5, 8, 12, 14, 15, 17, 18, 20, 34], Kari North (University of North Carolina Chapel Hill)[1, 3, 9, 10, 13, 15, 17, 34], Ulrike Peters (Fred Hutchinson Cancer Research Center)[1, 3, 11, 12, 13, 15, 17, 18, 34], Christopher S. Carlson (Fred Hutchinson Cancer Research Center, University of Washington)[1, 2, 3, 5, 12, 13, 14, 15, 16, 17, 18, 19, 34], Garnet Anderson (Fred Hutchinson

Cancer Research Center)[34], Hoda Anton-Culver (University of California at Irvine)[34], Themistocles L. Assimes (Stanford University School of Medicine)[5, 9, 11, 34], Paul L. Auer (Fred Hutchinson Cancer Research Center)[1, 2, 3, 5, 11, 12, 13, 15, 16, 18, 34], Shirley Beresford (Fred Hutchinson Cancer Research Center)[34], Chris Bizon (University of North Carolina Chapel Hill)[3, 9, 13, 15, 34], Henry Black (Rush Medical Center)[34], Robert Brunner (University of Nevada)[34], Robert Brzyski (University of Texas Health Science Center San Antonio)[34], Dale Burwen (National Heart, Lung, and Blood Institute WHI Project Office)[34], Bette Caan (Kaiser Permanente Division of Research, Oakland, CA)[34], Cara L. Carty (Fred Hutchinson Cancer Research Center)[18, 34], Rowan Chlebowski (Los Angeles Biomedical Research Institute)[34], Steven Cummings (University of California at San Francisco)[34], J. David Curb* (University of Hawaii)[9, 18, 34], Charles B. Eaton (Brown University, Memorial Hospital of Rhode Island)[12, 34], Leslie Ford (National Heart, Lung, and Blood Institute, National Heart, Lung, and Blood Institute WHI Project Office)[34], Nora Franceschini (University of North Carolina Chapel Hill)[2, 3, 9, 10, 15, 34], Stephanie M. Fullerton (University of Washington)[6, 11, 34], Margery Gass (University of Cincinnati)[34], Nancy Geller (National Heart, Lung, and Blood Institute WHI Project Office)[34], Gerardo Heiss (University of North Carolina Chapel Hill)[5, 34], Barbara V. Howard (Howard University, MedStar Research Institute)34, Li Hsu (Fred Hutchinson Cancer Research Center)[1, 13, 15, 18, 34], Carolyn M. Hutter (Fred Hutchinson Cancer Research Center)[13, 15, 18, 34], John Ioannidis (Stanford University School of Medicine)[11, 34], Shuo Jiao (Fred Hutchinson Cancer Research Center)[34], Karen C. Johnson (University of Tennessee Health Science Center)[3, 34], Charles Kooperberg (Fred Hutchinson Cancer Research Center)[1, 5, 9, 13, 14, 15, 17, 18, 34], Lewis Kuller (University of Pittsburgh)[34], Andrea LaCroix (Fred Hutchinson Cancer Research Center)[34], Kamakshi Lakshminarayan (University of Minnesota)[18, 34], Dorothy Lane (State University of New York at Stony Brook)[34], Ethan M. Lange (University of North Carolina Chapel Hill)[3, 5, 9, 13, 34], Leslie A. Lange (University of North Carolina Chapel Hill)[1, 2, 3, 5, 9, 12, 13, 15, 17, 18, 20, 25, 34], Norman Lasser (University of Medicine and Dentistry of New Jersey)[34], Erin LeBlanc (Kaiser Permanente Center for Health Research, Portland, OR)[34], Cora E. Lewis (University of Alabama at Birmingham)[25,34], Kuo-Ping Li (University of North Carolina Chapel Hill)[9, 34], Marian Limacher (University of Florida)[34], Dan-Yu Lin (University of North Carolina Chapel Hill)[1, 3, 9, 13, 15, 34], Benjamin A. Logsdon (Fred Hutchinson Cancer Research Center)[2, 34], Shari Ludlam (National Heart, Lung, and Blood Institute WHI Project Office)[34], JoAnn E. Manson (Brigham and Women's Hospital, Harvard School of Public Health)[34], Karen Margolis (University of Minnesota)[34], Lisa Martin (George Washington University Medical Center)[9, 34], Joan McGowan (National Heart, Lung, and Blood Institute WHI Project Office)[34], Keri L. Monda (Amgen, Inc.)[1, 15, 34], Jane Morley Kotchen (Medical College of Wisconsin)[34], Lauren Nathan (University of California Los Angeles)[34], Judith Ockene (Fallon Clinic, University of Massachusetts)[34], Mary Jo O'Sullivan (University of Miami)[34], Lawrence S. Phillips (Emory University)[34], Ross L. Prentice (Fred Hutchinson Cancer Research Center)[34], Alexander P. Reiner (Fred Hutchinson Cancer Research Center, University of Washington)[1, 2, 3, 5, 9, 11, 12, 13, 14, 15, 20, 25, 34], John Robbins (University of California at Davis)[34], Jennifer G. Robinson (University of Iowa)[9, 11, 18, 34], Jacques E. Rossouw (National Heart, Lung, and Blood Institute, National Heart, Lung, and Blood Institute WHI Project Office)[5, 14, 17, 20, 34], Haleh Sangi-Haghpeykar (Baylor College of Medicine)[34], Gloria E. Sarto (University of Wisconsin)[34], Sally Shumaker (Wake Forest University)[34], Michael S. Simon (Wayne State University)[34], Marcia L. Stefanick (Stanford University School of Medicine)[34], Evan Stein (Medical Research Labs)[34], Hua Tang (Stanford University)[2, 34], Kira C. Taylor (University of Louisville)[1, 3, 13, 15, 20, 34], Cynthia A. Thomson (University of Arizona)[34], Timothy A. Thornton (University of Washington)[13, 15, 18, 34], Linda Van Horn (Northwestern University)[34], Mara Vitolins (Wake Forest University)[34], Jean Wactawski-Wende (University of Buffalo)[34], Robert Wallace (University of Iowa)[2, 34], Sylvia Wassertheil-Smoller (Boston University)[18, 34], Donglin Zeng (University of North Carolina Chapel Hill)[9, 34]
*deceased

NHLBI GO ESP Project Team

Deborah Applebaum-Bowden (National Heart, Lung, and Blood Institute)[4, 7, 12, 17], Michael Feolo (National Center for Biotechnology Information)[12], Weiniu Gan (National Heart, Lung, and Blood Institute)[7, 8, 16, 17], Dina N. Paltoo (National Heart, Lung, and Blood Institute)[4, 6, 11, 17], Jacques E. Rossouw (National Heart, Lung, and Blood Institute, National Heart, Lung, and Blood Institute WHI Project Office)[5, 14, 17, 20, 34], Phyliss Sholinsky (National Heart, Lung, and Blood Institute)[4, 12, 17], Anne Sturcke (National Center for Biotechnology Information)[12]

ESP Groups

[1]Anthropometry Project Team, [2]Blood Count/Hematology Project Team, [3]Blood Pressure Project Team, [4]Data Flow Working Group, [5]Early MI Project Team, [6]ELSI Working Group, [7]Executive Committee, [8]Family Study Project Team, [9]Lipids Project Team, [10]Lung Project Team, [11]Personal Genomics Project Team, [12]Phenotype and Harmonization Working Group, [13]Population Genetics and Statistical Analysis Working Group, [14]Publications and Presentations Working Group, [15]Quantitative Analysis Ad Hoc Task Group, [16]Sequencing and Genotyping Working Group, [17]Steering Committee, [18]Stroke Project Team, [19]Structural Variation Working Group, [20]Subclinical/Quantitative Project Team

ESP Cohorts

[21]Acute Lung Injury (ALI), [22]Atherosclerosis Risk in Communities (ARIC), [23]Cardiovascular Health Study (CHS), [24]Chronic Obstructive Pulmonary Disease (COPDGene), [25]Coronary Artery Risk Development in Young Adults (CARDIA), [26]Cystic Fibrosis (CF), [27]Early Pseudomonas Infection Control (EPIC), [28]Framingham Heart Study (FHS), [29]Jackson Heart Study (JHS), [30]Lung Health Study (LHS), [31]Multi-Ethnic Study of Atherosclerosis (MESA), [32]Pulmonary Arterial Hypertension (PAH), [33]Severe Asthma Research Program (SARP), [34]Women's Health Initiative (WHI)

Supplemental Table 1: *VWF* coding sequence variants identified through the NHLBI Exome Sequencing Project.

VWF cDNA Position (NM_000552.3)	Variant Pos on Chr 12 (Build 37)	rs ID	Alleles (Build 37)*	MAF (%) EA	MAF (%) AA	VWF AA Position (of 2813)	GVS Function	AA Substitution	PolyPhen Prediction	GERP Score	Reported Phenotypic Associations	Refs.
21	12:6232342	rs144128523	G/A	0.0349	0	7	synonymous	none	unknown	-8.93		
22	12:6232341	unknown	C/T	0.0116	0.0227	8	missense	GLY,ARG	benign	-6.49		
81	12:6230479	rs140419498	G/A	0.0465	0.0454	27	synonymous	none	unknown	-11		1
96	12:6230464	rs146778712	C/T	0.0349	0	32	synonymous	none	unknown	-2.27		
97	12:6230463	unknown	C/G	0	0.0454	33	missense	ALA,PRO	possibly-damaging	4.4		
107	12:6230453	unknown	C/T	0	0.0227	36	missense	SER,ASN	probably-damaging	4.38		
114	12:6230446	rs149482309	G/A	0.4884	0.0454	38	synonymous	none	unknown	-6.32		1
135	12:6230425	unknown	G/A	0.0116	0	45	synonymous	none	unknown	1.33		
162	12:6230398	rs148741727	C/A	0.0116	0	54	synonymous	none	unknown	-5.88		
165	12:6230395	unknown	T/A	0.0116	0	55	synonymous	none	unknown	-3.4		
189	12:6230371	rs144310330	C/T	0.0116	0	63	synonymous	none	unknown	3.03		
250	12:6220105	unknown	G/A	0.0116	0	84	missense	LEU,PHE	probably-damaging	4.3		
255	12:6220100	unknown	G/A	0.0116	0.0227	85	synonymous	none	unknown	-2.96		
256	12:6220099	rs140044866	C/T	0.0116	0.0454	86	missense	VAL,MET	probably-damaging	5.19		
304	**12:6220051**	**rs147514785**	**C/T**	**0.0116**	**0.5901**	**102**	**missense**	**VAL,MET**	**benign**	**2.3**		
327	12:6219745	unknown	G/A	0	0.0227	109	synonymous	none	unknown	4.07		
338	12:6219734	unknown	T/C	0.0116	0	113	missense	TYR,CYS	probably-damaging	5.9		
385	**12:6219687**	**rs61753991**	**G/T**	**0**	**0.8171**	**129**	**missense**	**LEU,MET**	**possibly-damaging**	**3.73**	**Type 1 VWD**	**1-4**
390	**12:6219682**	**rs2229444**	**G/A**	**0.0581**	**1.5887**	**130**	**synonymous**	**none**	**unknown**	**2.94**		**1;4**
391	**12:6219681**	**rs76505074**	**C/T**	**0.0698**	**1.7022**	**131**	**missense**	**GLY,SER**	**benign**	**4.67**		**1;3**
409	12:6219663	rs71582882	C/A	0	0.3858	137	missense	VAL,LEU	benign	4.92		1
418	12:6219654	rs148218885	T/C	0	0.0454	140	missense	ILE,VAL	benign	4.65		
467	12:6219605	unknown	T/C	0.0116	0	156	missense	ASN,SER	probably-damaging	5.81		

NA	12:6219549	unknown	A1/R A1: T R: TCA	0.0121	0	NA	frameshift	none	unknown	5.81		
537	12:6204746	unknown	G/A	0	0.0227	179	synonymous	none	unknown	1.89		
545	12:6204738	unknown	G/A	0.0116	0	182	missense	SER,LEU	probably-damaging	3.89		
546	12:6204737	rs143054357	C/T	0.2326	0.0227	182	synonymous	none	unknown	-9.71		
605	12:6204678	unknown	C/T	0.0116	0	202	missense	ARG,GLN	probably-damaging	4.85		
623	12:6204660	unknown	C/G	0.0116	0	208	missense	SER,THR	benign	-4.81		4
682	12:6184693	unknown	G/A	0.0116	0	228	synonymous	none	unknown	2.84		
695	12:6184680	unknown	G/A	0	0.0227	232	missense	SER,LEU	probably-damaging	4.71		
706	12:6184669	rs140912382	G/A	0.0116	0.0454	236	missense	ARG,CYS	probably-damaging	4.71		
709	12:6184666	unknown	A/T	0.0116	0	237	missense	CYS,SER	probably-damaging	4.71		
727	12:6184648	unknown	G/A	0	0.0227	243	missense	PRO,SER	probably-damaging	4.71		
728	12:6184647	unknown	G/A	0.0116	0	243	missense	PRO,LEU	probably-damaging	4.71		
730	12:6184645	rs137987854	C/T	0.0116	0	244	missense	GLU,LYS	probably-damaging	3.79		
NA	12:6184594	unknown	A1/R A1: GC R: G	0.0242	0	NA	frameshift	none	unknown	0.17		
790	12:6184585	rs145476045	C/T	0.0116	0	264	missense	ALA,THR	benign	-9.42		
799	12:6184576	rs140388695	C/T	0.0116	0	267	missense	ALA,THR	benign	1.83		
817	12:6184558	rs61753997	G/A	0.0116	0	273	missense	ARG,TRP	probably-damaging	4.71	Type 1,3 VWD	1;4-6
850	12:6184525	unknown	C/T	0	0.0227	284	missense	GLY,SER	possibly-damaging	4.84		
869	12:6184506	unknown	G/A	0	0.0227	290	missense	ALA,VAL	benign	-0.35		
870	12:6184505	rs150192701	C/T	0	0.0454	290	synonymous	none	unknown	-9.69		
905	12:6182877	rs140911166	C/G	0.0116	0	302	missense	ARG,THR	benign	5.07		
925	12:6182857	unknown	C/A	0	0.0454	309	missense	ALA,SER	benign	-10.1		1

954	**12:6182828**	**rs1800387**	**A/T**	**2.5814**	**41.1711**	**318**	**missense**	**ASN,LYS**	**benign**	**-3.54**		1;4
974	12:6182808	rs11837584	C/A	0	0.3858	325	missense	CYS,PHE	probably-damaging	5.07		1
992	12:6182790	rs140004667	C/T	0	0.0227	331	missense	CYS,TYR	probably-damaging	5.07		
993	12:6182789	rs147924974	G/T	0	0.0227	331	stop-gained	CYS, stop	unknown	3.2		
1002	12:6181604	unknown	T/A	0	0.0227	334	synonymous	none	unknown	0.99		
1019	12:6181587	unknown	C/A	0.0116	0	340	missense	GLY,VAL	probably-damaging	0.37		
1037	**12:6181569**	**rs111971143**	**G/A**	**0.0233**	**1.3391**	**346**	**missense**	**THR,ILE**	**benign**	**5.55**		1;3
1050	12:6181556	rs141009309	G/A	0	0.0908	350	synonymous	none	unknown	-8.84		
1067	12:6181539	unknown	C/T	0.0233	0	356	missense	ARG,HIS	possibly-damaging	0.7		
1077	12:6181529	rs71582884	G/A	0.0814	0.0227	359	synonymous	none	unknown	-11.1		1
1091	12:6181515	unknown	G/A	0.0116	0	364	missense	SER,PHE	benign	2.66		
1106	12:6181500	unknown	G/A	0.0116	0	369	missense	THR,ILE	probably-damaging	5.55		
1107	12:6181499	rs149640698	G/C	0	0.1135	369	synonymous	none	unknown	2.31		
1157	12:6174439	unknown	C/A	0.0116	0	386	missense-near-splice	GLY,VAL	possibly-damaging	4.98		
1173	**12:6174423**	**rs1800375**	**T/A**	**12.6977**	**46.6409**	**391**	**synonymous**	**none**	**unknown**	**-5.91**		1;4
1179	12:6174417	unknown	T/C	0.0116	0	393	synonymous	none	unknown	-9.97		
1182	**12:6174414**	**rs1800376**	**T/G**	**12.6977**	**49.4326**	**394**	**synonymous**	**none**	**unknown**	**2.08**		1;4
NA	12:6174356	unknown	A1/R A1: GC R: G	0.0121	0	NA	frameshift	none	unknown	1.06		
1240	12:6174356	unknown	G/T	0	0.0227	414	missense	LEU,MET	probably-damaging	1.06		
1247	12:6174349	rs137950753	C/T	0	0.0227	416	missense	ARG,GLN	benign	0.1		1
1283	12:6174313	unknown	T/A	0.0116	0	428	missense	GLU,VAL	probably-damaging	4.98		
1306	12:6173538	rs145443126	G/A	0	0.1135	436	missense	ARG,CYS	possibly-damaging	4.53		3
1311	12:6173533	unknown	G/A	0.0116	0	437	synonymous	none	unknown	-3.97		

1319	12:6173525	unknown	C/T	0	0.0227	440	missense	CYS,TYR	probably-damaging	4.53		
1324	12:6173520	rs148247755	G/A	0.0116	0	442	missense	ARG,CYS	probably-damaging	4.53		
1325	12:6173519	unknown	C/T	0.0233	0	442	missense	ARG,HIS	probably-damaging	4.53	Type 2M VWD	7
1329	12:6173515	rs142404899	G/A	0.0349	0	443	synonymous	none	unknown	-9.07		1
1330	12:6173514	rs149116506	C/T	0	0.0227	444	missense	VAL,ILE	probably-damaging	4.53		
1339	12:6173505	unknown	G/A	0.0116	0	447	missense	ARG,TRP	probably-damaging	4.53		
1343	12:6173501	unknown	A/G	0	0.0227	448	missense	LEU,PRO	probably-damaging	4.53		
1393	12:6173451	unknown	C/G	0.0116	0	465	missense	ALA,PRO	possibly-damaging	2.37		
1410	12:6173434	rs111867665	G/A	0	0.0908	470	synonymous	none	unknown	-3.19		
1411	**12:6173433**	**rs1800377**	**C/T**	**11.0233**	**13.8675**	**471**	**missense**	**VAL,ILE**	**benign**	**-2.9**		1;4
1441	12:6172212	unknown	G/A	0.0233	0	481	missense	ARG,CYS	probably-damaging	3.93		1
1451	**12:6172202**	**rs1800378**	**T/C**	**34.314**	**21.9246**	**484**	**missense**	**HIS,ARG**	**possibly-damaging**	**1.25**		1;4
1452	12:6172201	rs147913451	A/T	0	0.0227	484	missense	HIS,GLN	possibly-damaging	2.83		
1456	12:6172197	unknown	C/T	0.0116	0	486	missense	VAL,MET	probably-damaging	3.04		
1461	12:6172192	unknown	C/T	0.0116	0	487	synonymous	none	unknown	2		
1463	12:6172190	rs144817575	G/C	0.0116	0.2043	488	missense	ALA,GLY	benign	0.59		1;3
1467	12:6172186	unknown	G/A	0.0116	0	489	synonymous	none	unknown	-6.75		
1471	12:6172182	unknown	G/A	0.0116	0	491	missense	ARG,CYS	probably-damaging	4.88		
1483	12:6172170	unknown	C/T	0	0.0227	495	missense	GLY,ARG	possibly-damaging	1.33		
1514	12:6172139	rs139830291	C/T	0.0349	0.0454	505	missense	ARG,HIS	probably-damaging	5.18		
1515	12:6172138	unknown	G/A	0.0116	0	505	synonymous	none	unknown	-10.4		
1516	12:6172137	unknown	C/T	0	0.0227	506	missense	GLY,ARG	probably-damaging	5.18		1
1548	**12:6167196**	**rs1800379**	**G/A**	**35.0769**	**41.2608**	**516**	**synonymous**	**none**	**unknown**	**-1.81**		1;4

1551	12:6167193	rs142956629	G/T	0	0.0682	517	synonymous	none	unknown	-9.79		
1596	**12:6167148**	**rs111240043**	**G/A**	**0.0233**	**0.6809**	**532**	**synonymous**	**none**	**unknown**	**-9.66**		**1**
1613	12:6167131	rs139196998	G/A	0	0.0227	538	missense	PRO,LEU	probably-damaging	4.94		1
1614	12:6167130	rs138268387	G/A	0.0582	0.0681	538	synonymous	none	unknown	-2.83		1;4
1625	**12:6167119**	**rs141649383**	**G/C**	**0.093**	**0**	**542**	**missense**	**ALA,GLY**	**possibly-damaging**	**-0.4**	**Type 3 VWD**	
1626	12:6167118	rs35365059	C/T	8.593	3.8584	542	synonymous	none	unknown	-0.29		1;4
1638	12:6167106	unknown	C/T	0	0.0227	546	synonymous	none	unknown	1.99		
1681	12:6167063	unknown	C/T	0.0116	0	561	missense	ASP,ASN	probably-damaging	3.81		
1722	12:6167022	unknown	C/T	0.0233	0	574	synonymous	none	unknown	1.4		
1728	12:6167016	rs150146744	C/A	0.0233	0.0227	576	missense-near-splice	MET,ILE	benign	1.43	Type 1 VWD	1;2;4
1753	12:6166215	rs141777100	C/T	0	0.1172	585	missense	ALA,THR	probably-damaging	-0.07		
1776	12:6166192	unknown	G/A	0	0.0235	592	synonymous	none	unknown	4.05		
1794	**12:6166174**	**rs35302737**	**G/A**	**0.0716**	**5.9507**	**598**	**synonymous**	**none**	**unknown**	**-9.92**		**1**
1817	12:6166151	unknown	C/T	0	0.2431	606	missense	ARG,GLN	benign	-3.72		
1848	12:6166120	unknown	C/G	0.0126	0	616	synonymous	none	unknown	-9.19		
1892	12:6166076	unknown	G/A	0.029	0.1659	631	missense	ALA,VAL	probably-damaging	4.05		3
1922	12:6166046	unknown	G/A	0.075	0.148	641	missense	ALA,VAL	possibly-damaging	-5.89	Type 1 VWD	4;8;9
2071	12:6161824	unknown	G/T	0.0233	0.0227	691	missense	PRO,THR	probably-damaging	2.93		
2094	12:6161801	rs141590700	C/T	0	0.0227	698	synonymous	none	unknown	-1.64		
2098	12:6161797	unknown	C/G	0.0116	0	700	missense	ASP,HIS	benign	-2.31		
2103	12:6161792	rs78995469	G/A	0.0116	0.4766	701	synonymous	none	unknown	-4.65		1
2108	12:6161787	unknown	G/A	0.0233	0	703	missense	PRO,LEU	probably-damaging	4.77		
2134	12:6161761	unknown	C/T	0.0116	0	712	missense	ASP,ASN	probably-damaging	4.77		
2136	12:6161759	rs146468788	G/A	0	0.0908	712	synonymous	none	unknown	-4.21		

2176	12:6161719	unknown	G/A	0.0116	0	726	missense	HIS,TYR	probably-damaging	4.77		
2207	12:6155963	rs149168790	A/G	0	0.0227	736	missense	MET,THR	benign	3.46		
2220	12:6155950	rs16932374	C/T	0.093	18.0663	740	missense	MET,ILE	benign	-2.93	Type 1,2M VWD	1;3;4;8-10
2233	12:6155937	unknown	C/T	0.0116	0.0227	745	missense	GLY,ARG	probably-damaging	3.46		
2295	12:6153604	rs150043098	T/C	0	0.0908	765	synonymous	none	unknown	-2.42		1
2305	12:6153594	rs143145764	G/A	0	0.0681	769	missense	PRO,SER	benign	2.14		
2312	12:6153587	unknown	A/G	0	0.0227	771	missense	MET,THR	probably-damaging	4.11		1
2332	12:6153567	rs146892641	C/T	0	0.0681	778	missense	ALA,THR	benign	3.27		
2340	**12:6153559**	**rs143904314**	**G/C**	**0**	**0.1816**	**780**	**missense**	**ASN,LYS**	**benign**	**3.27**		
2344	12:6153555	rs61748471	G/A	0.0116	0.0454	782	missense	ARG,TRP	possibly-damaging	0.94	Type 2N VWD	4;7;11
2345	12:6153554	rs61748472	C/G	0.0116	0	782	missense	ARG,PRO	probably-damaging	-1.37		
2365	**12:6153534**	**rs1063856**	**T/C**	**35.7442**	**43.1684**	**789**	**missense**	**THR,ALA**	**benign**	**2.17**	**High VWF, risk CHD, VT**	**1;4;12-14**
2385	12:6153514	rs1063857	A/G	35.7558	43.1911	795	synonymous	none	unknown	-5.47		1
2389	12:6153510	unknown	G/A	0.0233	0.0227	797	synonymous	none	unknown	1.08		
2409	12:6153490	unknown	G/C	0.0116	0	803	synonymous	none	unknown	3.2		
2451	**12:6145649**	**rs57950734**	**A/T**	**0.0349**	**11.6659**	**817**	**missense**	**HIS,GLN**	**probably-damaging**	**-0.03**	**Type 2N**	**1;3;4;7;11**
2477	12:6145623	unknown	C/T	0.0116	0	826	missense	ARG,LYS	benign	4.97		
2478	12:6145622	unknown	C/G	0.0116	0	826	missense	ARG,SER	probably-damaging	-1.62		
2510	**12:6145590**	**rs75645183**	**G/T**	**0**	**2.2015**	**837**	**missense**	**ALA,ASP**	**benign**	**3.05**		**1;3**
2513	12:6145587	rs149520234	G/A	0	0.0454	838	missense	PRO,LEU	probably-damaging	4.04		
2536	12:6145564	unknown	A/C	0.0233	0	846	missense	CYS,GLY	probably-damaging	4.79		
2555	12:6143984	rs216321	C/T	8.9302	5.0386	852	missense	GLN,ARG	benign	0.42		1;4
2561	12:6143978	rs41276738	C/T	0.5581	0.0454	854	missense	ARG,GLN	probably-damaging	5.56	Type 1,2N	1-4;7;8;15-17
2575	12:6143964	unknown	T/C	0	0.0227	859	missense	THR,ALA	possibly-damaging	4.38		
2586	12:6143953	rs34510401	C/A	0.0814	0	862	synonymous	none	unknown	2.76		1

2591	12:6143948	rs146405753	T/C	0	0.0227	864	missense	ASP,GLY	possibly-damaging	5.56		
2603	12:6143936	unknown	G/C	0	0.0227	868	missense	SER,CYS	probably-damaging	5.56		
2610	**12:6143929**	**rs141982646**	**G/A**	**0**	**0.3631**	**870**	**synonymous**	**none**	**unknown**	**-3.59**		**1**
2611	12:6143928	rs148122508	C/T	0	0.0227	871	missense	GLY,SER	probably-damaging	5.56		
2626	**12:6143913**	**rs143762054**	**G/A**	**0**	**0.1362**	**876**	**missense**	**LEU,PHE**	**benign**	**2.72**		
2632	12:6143907	rs148969007	A/T	0	0.0227	878	missense	PHE,ILE	probably-damaging	5.45		
2651	12:6143888	rs146850658	A/C	0	0.0227	884	missense	LEU,ARG	benign	4.1		
2662	12:6143877	unknown	C/G	0	0.0227	888	missense	GLU,GLN	benign	3.22		
2674	12:6143865	unknown	C/T	0	0.0227	892	missense	VAL,ILE	benign	4.57		1
NA	12:6140736	unknown	A1/R A1: G R: GCAGTAA TCCT	0.0242	0	NA	frameshift-near-splice	none	unknown	-1.38		
2695	12:6140735	rs142135013	C/T	0	0.0227	899	missense	GLY,SER	benign	5.58		1
2739	**12:6140691**	**rs35191786**	**T/G**	**0.0233**	**0.1816**	**913**	**synonymous**	**none**	**unknown**	**-3.11**		**1;4**
2771	12:6140659	rs33978901	C/T	2.1163	0.2951	924	missense	ARG,GLN	probably-damaging	3.75	Type1,2N	1-4;8;18
2775	12:6140655	unknown	A/G	0	0.0227	925	synonymous	none	unknown	4.67		
2785	12:6140645	unknown	C/T	0	0.0227	929	missense	VAL,MET	benign	-0.15		
2801	12:6140629	rs142563352	A/G	0	0.0227	934	missense	ILE,THR	possibly-damaging	5.58		
2814	**12:6140616**	**rs139622018**	**G/A**	**0.0233**	**0.1589**	**938**	**synonymous**	**none**	**unknown**	**-10.1**		**1**
2815	12:6140615	rs147408448	C/T	0	0.0227	939	missense	GLY,ARG	probably-damaging	4.7		1
2839	12:6138636	rs142861582	T/C	0.0116	0.0227	947	missense	MET,VAL	benign	-3.8		1
2863	12:6138612	unknown	C/A	0	0.0227	955	missense	VAL,LEU	possibly-damaging	3.67		
2878	12:6138597	unknown	G/A	0	0.0227	960	missense	ARG,TRP	probably-damaging	4.58		
2880	12:6138595	rs1800380	C/T	25.1395	31.1621	960	synonymous	none	unknown	-5.07		1;4
2895	12:6138580	rs144225315	C/G	0	0.0227	965	synonymous	none	unknown	2.54		1
2899	12:6138576	rs149573046	C/T	0	0.0227	967	missense	GLY,SER	benign	3.69		

2900	**12:6138575**	**rs141087261**	**C/T**	**0**	**2.4739**	**967**	**missense**	**GLY,ASP**	**benign**	**3.69**		[3]
2906	12:6138569	unknown	G/A	0	0.0227	969	missense	ALA,VAL	possibly-damaging	1.41		[1]
2913	12:6138562	unknown	G/A	0.0116	0	971	synonymous	none	unknown	-9.16		[4]
2914	12:6138561	rs150418484	C/T	0.0116	0	972	missense	VAL,MET	probably-damaging	2.65		
2943	12:6138532	unknown	G/A	0.0116	0.0227	981	synonymous	none	unknown	-9.16		
2944	12:6138531	unknown	C/G	0.0116	0	982	missense	VAL,LEU	probably-damaging	4.58		
3008	12:6135172	rs141477932	T/C	0.0233	0	1003	missense	GLN,ARG	probably-damaging	4.84		
3013	12:6135167	unknown	T/C	0.0116	0	1005	missense	ASN,ASP	probably-damaging	4.84		
3022	12:6135158	rs138940478	T/C	0.0116	0	1008	missense	THR,ALA	probably-damaging	4.84		
3023	12:6135157	unknown	G/T	0.0116	0	1008	missense	THR,ASN	probably-damaging	4.84		
3087	12:6135093	unknown	C/T	0.0116	0	1029	synonymous	none	unknown	-4.29		
3089	**12:6135091**	**rs145125264**	**T/C**	**0**	**0.749**	**1030**	**missense**	**GLN,ARG**	**probably-damaging**	**2.27**		[1;3]
3092	12:6135088	rs141412860	C/T	0	0.0227	1031	missense	CYS,TYR	probably-damaging	4.69		
3103	12:6135077	rs146648301	T/C	0.0116	0	1035	missense	ARG,GLY	benign	2.26		[1]
NA	12:6135076	unknown	A1/R A1: C R: CTGG	0.1696	1.5002	NA	coding	none	unknown	-0.97		
3175	12:6134793	unknown	A/G	0.0117	0	1059	missense	SER,PRO	possibly-damaging	2.12		
3232	12:6132944	unknown	C/T	0.0116	0	1078	missense	GLU,LYS	probably-damaging	5.11	Type 2N	[4]
3240	**12:6132936**	**rs4021576**	**A/G**	**0**	**6.0046**	**1080**	**synonymous**	**none**	**unknown**	**4.22**		[4]
3281	12:6132895	unknown	A/G	0.0116	0	1094	missense	ILE,THR	possibly-damaging	5.11	Type 1	[8]
3291	12:6132885	rs149895348	G/A	0.0116	0.0456	1097	synonymous	none	unknown	-10.2		
3303	12:6132873	unknown	G/A	0	0.0228	1101	synonymous	none	unknown	-10.2		
3365	12:6132811	unknown	G/A	0.0116	0	1122	missense	THR,MET	probably-damaging	4.21		[1]

3366	12:6132810	unknown	C/T	0	0.0227	1122	synonymous	none	unknown	-10.2		
3379	12:6132797	rs139579968	G/A	0.0116	0	1127	missense-near-splice	PRO,SER	probably-damaging	5.11		
3547	12:6131193	rs147818186	G/C	0.0116	0	1183	missense	LEU,VAL	probably-damaging	3.8		
3549	12:6131191	rs144447692	C/G	0.0116	0	1183	synonymous	none	unknown	4.69		
3570	12:6131170	unknown	G/A	0.0116	0	1190	synonymous	none	unknown	1.82		
3571	12:6131169	unknown	C/T	0	0.0227	1191	missense	VAL,ILE	benign	-3.38		
3579	**12:6131161**	**rs16933969**	**A/G**	**0.1047**	**21.9246**	**1193**	**synonymous**	**none**	**unknown**	**-3.61**		1;4
3583	12:6131157	unknown	C/A	0.0116	0	1195	missense	ASP,TYR	probably-damaging	4.74	Type 2A	
3590	12:6131150	unknown	G/A	0.0116	0	1197	missense	PRO,LEU	probably-damaging	4.74		
3594	12:6131146	unknown	C/A	0.0116	0	1198	synonymous	none	unknown	3.85		
3613	12:6131127	unknown	G/A	0.0116	0	1205	missense	ARG,CYS	probably-damaging	4.74		
3686	12:6128898	unknown	A/C	0.0117	0.2499	1229	missense	VAL,GLY	benign	4.94	Type 1	2-4
3692	12:6128892	unknown	T/C	0.0466	0	1231	missense	ASN,SER	benign	2.59	Type 1	2-4
3719	12:6128865	rs150576611	G/A	0.0466	0.0228	1240	missense	PRO,LEU	benign	4.02		
3720	12:6128864	rs141792415	C/T	0.035	0	1240	synonymous	none	unknown	-9.28		
3735	12:6128849	rs148499318	C/T	0.1289	0.0457	1245	synonymous	none	unknown	1.82		
3789	12:6128795	unknown	C/T	0.0233	0	1263	synonymous	none	unknown	-9.88		4
3795	**12:6128789**	**rs2228319**	**C/T**	**0.0465**	**11.8248**	**1265**	**synonymous**	**none**	**unknown**	**-5.52**		1;4
3797	12:6128787	rs61749370	G/T	0.0116	0	1266	missense	PRO,GLN	probably-damaging	5.15	Type 2B	2;4
3835	12:6128749	rs61749376	C/T	0.0465	0	1279	missense	VAL,ILE	possibly-damaging	5.15	Type 1,2A,2B,2M,3	2;4
3867	12:6128717	unknown	G/A	0.0116	0	1289	synonymous	none	unknown	-10.3		
3868	12:6128716	rs138900040	C/T	0	0.2951	1290	missense	GLU,LYS	probably-damaging	3.26		
3944	12:6128640	rs61749396	C/T	0.0116	0	1315	missense	ARG,HIS	probably-damaging	4.98	Type 1	4;8
3945	12:6128639	rs143009893	G/A	0.0116	0	1315	synonymous	none	unknown	-9.96		
3952	12:6128632	unknown	C/T	0	0.0227	1318	missense	VAL,MET	probably-damaging	-1.18		

3967	12:6128617	unknown	C/T	0.0116	0	1323	missense	ASP,ASN	probably-damaging	4.98		
3987	12:6128597	rs138413641	G/C	0	0.0227	1329	missense	ILE,MET	benign	-5.44		
4011	12:6128573	rs1800381	C/T	0	0.0227	1337	synonymous	none	unknown	-6.83		1
4024	12:6128560	rs61749404	G/A	0	0.0908	1342	missense	ARG,CYS	probably-damaging	4.98	Type 1	3;8
4027	12:6128557	rs150923481	T/C	0.0116	0.0227	1343	missense	ILE,VAL	benign	1.29		
4050	**12:6128534**	**rs143459496**	**C/T**	**0**	**0.1589**	**1350**	**synonymous**	**none**	**unknown**	**-2.22**		
4092	12:6128492	unknown	T/C	0.0116	0	1364	synonymous	none	unknown	-2.08		
4103	12:6128481	unknown	A/G	0.0233	0	1368	missense	ILE,THR	benign	4.98		
4130	**12:6128454**	**rs141211612**	**G/A**	**0**	**0.2724**	**1377**	**missense**	**ALA,VAL**	**probably-damaging**	**4.08**		4
4138	**12:6128446**	**rs11063988**	**T/C**	**0.0349**	**10.6219**	**1380**	**missense**	**ILE,VAL**	**benign**	**-3.75**		4
4141	12:6128443	rs216311	T/C	38.0116	11.8021	1381	missense	THR,ALA	benign	0.2		4
4146	12:6128438	rs140464171	C/A	0.093	0	1382	synonymous	none	unknown	4.09		
NA	12:6128418	rs63749068	A1/A2/A3/R A1: TCCTGGCTGGCCATCAGGAGCAGGGCGATGCGGGAGGCTTCAGGGCGGTCGATCTTGCTGCAGATTTGGA A2: TCCTGGCTGGCCATCAGGAGCAGGGCGATGCGGGAGGCTTCAGGGCGGTCGATCTTGCTGAAGATTTGGAACAGTG	28.9288	35.1625	NA	codingComplex	none	unknown	4.98	In A1	

			A3: TCCTGGCTGGCCATCAGGAGCAGGGCGACGCGGGAGGCTTCAGGGCGGTCGATCTTGCTGAAGATTTGGAACAGTG R: T									
4173	12:6128411	rs145009516	T/C	0.035	0	1391	synonymous	none	unknown	-9.83		4
4182	12:6128402	rs139215659	G/A	0	0.0227	1394	synonymous	none	unknown	0.85		
4196	12:6128388	rs1800382	C/T	1.4073	0.2951	1399	missense	ARG,HIS	benign	4.03		4
4206	12:6128378	unknown	C/T	0	0.0227	1402	synonymous	none	unknown	1.81		
4222	12:6128362	rs141990425	T/G	0	0.0227	1408	missense	LYS,GLN	probably-damaging	4.92		
NA	12:6128359	rs61750078	A1/R A1: C R: CCTT	0.0485	0.0469	NA	coding	none	unknown	4		
4255	12:6128329	unknown	G/T	0.0116	0	1419	missense	HIS,ASN	benign	4.92		
4281	12:6128303	rs140077306	G/A	0.0116	0	1427	synonymous	none	unknown	3.71		
4285	12:6128299	unknown	C/T	0.0233	0	1429	missense	GLU,LYS	possibly-damaging	4.35		
4304	**12:6128280**	**rs11063987**	**T/C**	**0.0233**	**10.3041**	**1435**	**missense**	**ASN,SER**	**possibly-damaging**	**4.35**		**1;4**
4315	**12:6128269**	**rs150077670**	**C/T**	**0.0116**	**0.3858**	**1439**	**missense**	**VAL,MET**	**benign**	**-1.93**		**1**
4353	12:6128231	unknown	G/A	0.0116	0	1451	synonymous	none	unknown	-5.73		
4413	12:6128171	unknown	G/A	0.0116	0	1471	synonymous	none	unknown	-3.78		
4414	**12:6128170**	**rs1800383**	**C/G**	**6.5744**	**39.3266**	**1472**	**missense**	**ASP,HIS**	**benign**	**0.81**		4
4443	12:6128141	rs144796763	C/A	0.1861	0.0228	1481	synonymous	none	unknown	0.31		
4457	**12:6128127**	**rs149424724**	**G/A**	**0.0116**	**0.8178**	**1486**	**missense**	**SER,LEU**	**benign**	**3**		**1**
4458	12:6128126	rs138966048	C/T	0	0.0227	1486	synonymous	none	unknown	-9.63		

4515	12:6128069	unknown	T/C	0.0116	0	1505	synonymous	none	unknown	-8.1		
4518	12:6128066	rs146928422	C/T	0.0116	0	1506	synonymous	none	unknown	-5.61		
4527	12:6128057	rs141174823	A/G	0	0.0454	1509	synonymous	none	unknown	-8.15		
4585	12:6127999	rs138670575	C/G	0	0.0227	1529	missense	ASP,HIS	benign	4.84		
4613	12:6127971	unknown	G/A	0.0116	0	1538	missense	THR,MET	possibly-damaging	4.11		
4659	12:6127925	unknown	G/A	0.0116	0	1553	synonymous	none	unknown	-9.18		
4665	**12:6127919**	**rs1800384**	**T/G**	**7.7791**	**2.2696**	**1555**	**synonymous**	**none**	**unknown**	**-9.99**		**4**
4690	12:6127894	unknown	G/A	0	0.0227	1564	missense	ARG,TRP	probably-damaging	2.97		
4693	12:6127891	rs1800385	C/A	8.0349	2.3377	1565	missense	VAL,LEU	benign	1.87		4
4716	12:6127868	unknown	G/A	0.0116	0	1572	synonymous	none	unknown	-9.99		4
4751	12:6127833	rs1800386	T/C	0.3023	0.0454	1584	missense	TYR,CYS	probably-damaging	5	Type 1	1-4;8;19
4757	12:6127827	unknown	G/A	0.0116	0	1586	missense	SER,PHE	probably-damaging	5		
4799	12:6127785	unknown	G/A	0.0116	0	1600	missense	ALA,VAL	benign	4.05		
4824	**12:6127760**	**rs142635883**	**G/A**	**0.0116**	**0.8625**	**1608**	**synonymous**	**none**	**unknown**	**-9.87**		**1**
4854	12:6127730	unknown	C/T	0	0.0227	1618	synonymous	none	unknown	-1.76		
4876	12:6127708	unknown	C/A	0.0116	0	1626	missense	VAL,LEU	benign	3.13		
4905	12:6127679	rs148901164	G/A	0.0116	0.0227	1635	synonymous	none	unknown	-9.08		
4906	12:6127678	rs145676400	C/T	0.0116	0.0454	1636	missense	VAL,MET	benign	-0.39		
4917	12:6127667	rs146596289	C/T	0	0.2724	1639	synonymous	none	unknown	5.03		1
4923	12:6127661	rs140001946	C/T	0	0.3404	1641	synonymous	none	unknown	-0.34		1
4968	12:6127616	rs143838793	C/T	0.0349	0	1656	synonymous	none	unknown	-6.03		
5014	12:6127570	rs61750598	C/T	0.0116	0.0228	1672	missense	GLY,ARG	possibly-damaging	2.25	Type 2A	1;4;20
5065	12:6126025	rs139320345	G/T	0.0116	0.0227	1689	missense	PRO,THR	probably-damaging	3.4		
5099	12:6125991	unknown	G/A	0.0116	0	1700	missense	SER,PHE	probably-damaging	4.31		
5129	12:6125961	unknown	A/G	0	0.0227	1710	missense	MET,THR	probably-damaging	4.31		
5139	12:6125951	rs150873446	G/A	0	0.227	1713	synonymous	none	unknown	-5.55		

5165	12:6125925	unknown	T/C	0.0116	0	1722	missense	ASN,SER	benign	3.15		
5173	**12:6125820**	**rs78302129**	**G/A**	**0**	**2.3377**	**1725**	**missense**	**PRO,SER**	**probably-damaging**	**3.39**		1;3
5177	12:6125816	rs147313320	C/T	0	0.1135	1726	missense	ARG,HIS	benign	-0.89		
5191	12:6125802	rs61750603	A/T	0.1977	0	1731	missense	SER,THR	probably-damaging	1.84	unclassified VWD	1;4
5200	12:6125793	unknown	G/A	0.0116	0	1734	stop-gained	GLN,stop	unknown	4.31		
5219	12:6125774	unknown	G/A	0	0.0227	1740	missense	THR,ILE	probably-damaging	3.4		
5269	12:6125724	unknown	G/A	0	0.0454	1757	missense	LEU,PHE	possibly-damaging	2.24		
5277	**12:6125716**	**rs41276736**	**G/A**	**1.2558**	**0.2043**	**1759**	**synonymous**	**none**	**unknown**	**-0.15**		1;4
5278	12:6125715	rs61750604	C/T	0.1628	0	1760	missense	VAL,ILE	benign	-0.01	Type 1	1;2
5288	12:6125705	unknown	C/T	0.0116	0	1763	missense	ARG,GLN	benign	-6.71		
5311	12:6125682	unknown	C/T	0	0.0227	1771	missense-near-splice	GLY,ARG	probably-damaging	4.34		
5313	**12:6125397**	**rs2229448**	**C/A**	**0.093**	**3.1775**	**1771**	**synonymous-near-splice**	**none**	**unknown**	**3.68**		1;4
5338	12:6125372	unknown	A/C	0	0.0227	1780	missense	TYR,ASP	probably-damaging	4.58		
5354	12:6125356	rs150349730	A/G	0	0.0227	1785	missense	MET,THR	benign	2.15		
5370	12:6125340	rs71582868	C/T	0.0116	0	1790	synonymous	none	unknown	-6.88		1
5384	12:6125326	rs146729537	G/A	0	0.227	1795	missense	ALA,VAL	benign	-3.44		1;3
5403	12:6125307	unknown	C/T	0.0116	0	1801	synonymous	none	unknown	-3.44		
5463	12:6122804	unknown	T/C	0	0.0227	1821	synonymous	none	unknown	-5.09		
5473	12:6122794	unknown	T/C	0	0.0227	1825	missense	ILE,VAL	benign	1.5		
5486	12:6122781	rs143445274	T/C	0	0.0227	1829	missense	ASP,GLY	probably-damaging	5.21		
5489	12:6122778	unknown	C/T	0	0.0227	1830	missense	ARG,HIS	probably-damaging	0.78		
5515	**12:6122752**	**rs141134620**	**A/G**	**0**	**2.2696**	**1839**	**synonymous**	**none**	**unknown**	**2.89**		
5518	12:6122749	unknown	C/A	0.0233	0	1840	missense	ALA,SER	probably-damaging	5.21		
5541	12:6122726	rs146540001	G/A	0.0116	0	1847	synonymous	none	unknown	-4.29		
5597	12:6122670	unknown	G/A	0	0.0227	1866	missense	SER,PHE	probably-damaging	4.28		

5631	12:6121286	rs144221902	C/T	0.0116	0	1877	synonymous	none	unknown	-5.42		
5667	**12:6120958**	**rs56981471**	**G/A**	**0.0589**	**6.023**	**1889**	**synonymous**	**none**	**unknown**	**-0.99**		**1;4**
5673	12:6120952	unknown	G/A	0.0117	0	1891	synonymous	none	unknown	-4.08		
5704	12:6120921	rs144757652	C/T	0	0.0228	1902	missense	VAL,MET	possibly-damaging	4.66		
5777	12:6120848	unknown	G/A	0	0.0227	1926	missense	SER,LEU	benign	4.14		
5785	12:6120840	rs149799233	T/A	0.0116	0	1929	missense	ASN,TYR	possibly-damaging	3.89		
5797	12:6120828	unknown	G/A	0	0.0227	1933	missense	PRO,SER	probably-damaging	3.13		
5801	12:6120824	rs139845585	A/C	0.0117	0	1934	missense	VAL,GLY	benign	5.03		
5844	**12:6105387**	**rs216902**	**G/A**	**37.9767**	**30.9805**	**1948**	**synonymous-near-splice**	**none**	**unknown**	**0.48**		**1;4**
5845	12:6105386	unknown	C/T	0.0116	0	1949	missense	VAL,MET	benign	-0.04		
5851	12:6105380	rs144072210	T/C	0.093	0.0227	1951	missense	THR,ALA	possibly-damaging	5.55		
5909	12:6105322	unknown	C/T	0.0116	0	1970	missense	GLY,ASP	probably-damaging	5.55		
6000	12:6105231	unknown	G/A	0.0116	0	2000	synonymous	none	unknown	3.66		
6016	12:6105215	rs140229844	C/T	0	0.0227	2006	missense	GLU,LYS	probably-damaging	4.6		
6052	12:6105179	unknown	T/C	0	0.0227	2018	missense	SER,GLY	possibly-damaging	2.97		1
6069	12:6103768	unknown	C/T	0	0.0454	2023	synonymous	none	unknown	-9.82		
6087	12:6103750	unknown	G/C	0	0.0454	2029	synonymous	none	unknown	0.3		
6099	12:6103738	rs55784921	G/A	0.186	0.0227	2033	synonymous	none	unknown	-1.54		1;4
6187	12:6103650	rs61750615	G/A	1.0698	0.2497	2063	missense	PRO,SER	probably-damaging	4.91	Type 1,3 (or no known pathogenicity)	1-4;8;9
6219	12:6103618	rs147982896	G/A	0.0116	0.0227	2073	synonymous	none	unknown	3.04		
6242	12:6103595	unknown	G/A	0.0116	0	2081	missense	THR,MET	benign	-5.64		
6250	12:6103587	unknown	G/C	0.0116	0	2084	missense	LEU,VAL	possibly-damaging	5.15		1
6277	12:6103349	rs149274687	C/G	0.0116	0	2093	missense	ALA,PRO	probably-damaging	3.11		
6302	12:6103324	unknown	C/T	0.0116	0	2101	missense	GLY,ASP	probably-damaging	5.17		

6303	12:6103323	rs115914543	G/T	0.0349	0.3631	2101	synonymous	none	unknown	1.16		1
6320	12:6103306	unknown	C/A	0	0.0227	2107	missense	TRP,LEU	benign	0.44		
6339	12:6103287	unknown	T/C	0.0116	0	2113	synonymous	none	unknown	-10.3		
6345	**12:6103281**	**rs11537642**	**A/T**	**0.0465**	**14.9796**	**2115**	**synonymous**	**none**	**unknown**	**-10.3**		**1**
6352	12:6103274	unknown	G/A	0.0116	0	2118	missense	ARG,TRP	benign	3.22		
6353	12:6103273	unknown	C/T	0	0.0454	2118	missense	ARG,GLN	benign	3.94		
6366	12:6103260	rs141097321	C/T	0	0.0227	2122	synonymous	none	unknown	-10.3		
6375	12:6103251	unknown	G/C	0.0116	0	2125	synonymous	none	unknown	-2.46		
6377	12:6103249	rs71579338	A/G	0.0116	0	2126	missense	ILE,THR	benign	2.8		4
6405	12:6103221	rs146529302	G/C	0	0.0227	2135	missense	ASP,GLU	benign	2.33		
6433	12:6103193	rs61750618	G/A	0	0.0227	2145	missense	PRO,SER	benign	0	Type 1	4;8
6463	12:6103163	unknown	C/T	0	0.0227	2155	missense	ALA,THR	possibly-damaging	4.39		
6532	**12:6103094**	**rs34230288**	**C/A**	**2.2558**	**0.3631**	**2178**	**missense**	**ALA,SER**	**benign**	**-0.72**		**1;4**
6554	**12:6103072**	**rs76342212**	**C/T**	**0.1512**	**19.9047**	**2185**	**missense**	**ARG,GLN**	**probably-damaging**	**5.3**	**Type 1**	**1-4**
6561	12:6103065	rs151250563	G/A	0.0116	0	2187	synonymous	none	unknown	-7.41		
6570	12:6103056	unknown	G/A	0.0116	0	2190	synonymous	none	unknown	1.54		
6674	12:6101109	rs142316574	C/T	0.0116	0	2225	missense	SER,ASN	possibly-damaging	3.75		
6677	12:6101106	unknown	G/T	0.0116	0.0227	2226	missense	SER,TYR	benign	3.76		1
6756	12:6101027	rs71581020	C/T	0.1628	0.0454	2252	synonymous	none	unknown	3.49		
6784	12:6100999	rs147715696	C/T	0	0.0227	2262	missense	GLY,ARG	probably-damaging	5.66		
6846	**12:6094784**	**rs10849371**	**T/C**	**14.8023**	**19.2919**	**2282**	**synonymous**	**none**	**unknown**	**1.04**		**1;4**
6859	**12:6094771**	**rs61750625**	**G/A**	**0**	**0.6128**	**2287**	**missense**	**ARG,TRP**	**probably-damaging**	**1.58**	**Type 1**	**1;4;8;9**
6894	12:6094736	rs147523582	C/T	0	0.0227	2298	synonymous	none	unknown	-9.6		
6908	12:6094279	rs149432685	G/A	0.0116	0	2303	missense	THR,MET	benign	4.44		
6909	12:6094278	unknown	C/T	0.0116	0	2303	synonymous	none	unknown	-10.7		
6916	12:6094271	rs138997660	G/A	0	0.0454	2306	synonymous	none	unknown	4.42		
6931	12:6094256	rs150725355	G/A	0.0349	0	2311	missense	ARG,CYS	probably-damaging	5.33	Type 1	4

6937	12:6094250	unknown	G/T	0.0116	0	2313	missense	ARG,SER	possibly-damaging	4.41		
6938	12:6094249	rs62641242	C/T	0.0116	0.0681	2313	missense	ARG,HIS	possibly-damaging	-2.61	Type 1	1;3;4;8
6949	12:6094238	rs138618444	C/T	0	0.0227	2317	missense	ASP,ASN	benign	0.1		
6965	12:6094222	unknown	T/A	0.0233	0	2322	missense	GLU,VAL	probably-damaging	5.33		
6978	12:6092419	unknown	C/T	0.0116	0	2326	synonymous-near-splice	none	unknown	2.87		
7007	12:6092390	rs144769404	G/A	0.0349	0	2336	missense	PRO,LEU	benign	-1.38		
7024	12:6092373	rs142612858	G/A	0.0116	0	2342	missense	ARG,CYS	benign	3.97		
7025	12:6092372	rs34120165	C/T	0.0116	0.0227	2342	missense	ARG,HIS	benign	-1.86		
7059	**12:6092338**	**rs112319661**	**C/G**	**0**	**0.5901**	**2353**	**missense**	**GLU,ASP**	**possibly-damaging**	**0.47**		1
7080	**12:6092317**	**rs111597150**	**G/A**	**0**	**0.1816**	**2360**	**synonymous-near-splice**	**none**	**unknown**	**-9.71**		1
7117	12:6091122	rs148908677	G/A	0.0116	0	2373	missense	PRO,SER	probably-damaging	4.83		
7130	12:6091109	unknown	G/A	0.0116	0.0227	2377	missense	PRO,LEU	probably-damaging	3.92		
7150	**12:6091089**	**rs145697622**	**G/A**	**0**	**0.2724**	**2384**	**missense**	**ARG,TRP**	**probably-damaging**	**4.1**		1;3
7151	12:6091088	rs150201871	C/T	0	0.0454	2384	missense	ARG,GLN	probably-damaging	2.19		
7173	12:6091066	unknown	C/T	0	0.0227	2391	synonymous	none	unknown	2.55		
7191	12:6091048	rs142422347	G/A	0	0.0454	2397	synonymous	none	unknown	4.62		
7207	12:6091032	rs147705313	C/T	0	0.0227	2403	missense	VAL,MET	possibly-damaging	3.56		
7236	12:6091003	rs145450160	T/G	0	0.1816	2412	synonymous	none	unknown	-11		
7239	**12:6091000**	**rs216867**	**A/G**	**10.5465**	**25.488**	**2413**	**synonymous**	**none**	**unknown**	**-7.54**		1;4
7281	12:6090958	rs151303589	G/A	0.0116	0	2427	synonymous	none	unknown	-5.03		
7301	12:6085413	unknown	C/T	0	0.0227	2434	missense	ARG,GLN	probably-damaging	-0.52		
7329	12:6085385	rs142444263	G/A	0	0.0227	2443	synonymous	none	unknown	5.38		
7344	12:6085370	rs55944252	G/A	0.0814	0	2448	synonymous	none	unknown	-7.4		1;4
7362	12:6085352	rs146504585	G/A	0.0116	0	2454	synonymous	none	unknown	-10.4		1

7377	**12:6085337**	**rs142452106**	**G/A**	**0**	**0.227**	**2459**	**synonymous**	**none**	**unknown**	**-10.4**		1
7378	12:6085336	rs149677556	C/T	0	0.0227	2460	missense	VAL,MET	probably-damaging	5.19		
7391	12:6085323	unknown	C/A	0.0116	0	2464	missense	ARG,LEU	possibly-damaging	3		
7392	12:6085322	rs149984396	G/A	0.0349	0	2464	synonymous	none	unknown	-10.4		1
7393	12:6085321	unknown	C/T	0	0.0227	2465	missense	VAL,MET	probably-damaging	5.19		
7433	12:6085281	rs111752224	C/T	0.0233	0	2478	missense	ARG,GLN	benign	-6.3		1
NA	12:6085276	rs61751290	C/A	0.0116	0	NA	splice-5	none	unknown	5.19		
7449	12:6080864	unknown	G/A	0.0116	0	2483	synonymous	none	unknown	-8.39		
7450	12:6080863	rs139864572	C/T	0.0116	0	2484	missense	VAL,ILE	possibly-damaging	4.79		
7518	12:6080795	unknown	C/T	0.0116	0.0227	2506	synonymous	none	unknown	-9.58		
7551	12:6078555	rs145955543	G/A	0.0233	0	2517	synonymous	none	unknown	-7.48		
7571	12:6078535	unknown	G/A	0	0.0227	2524	missense	PRO,LEU	benign	0.74		
7590	12:6078516	unknown	G/C	0	0.0227	2530	missense	ILE,MET	benign	4.87		
7603	12:6078503	rs61751296	G/A	0.0116	0	2535	stop-gained	ARG,stop	unknown	3.96	Type 3	4
7604	12:6078502	rs137987906	C/T	0.0116	0.0227	2535	missense	ARG,GLN	probably-damaging	3.98		
7619	12:6078487	rs150778949	A/G	0	0.1135	2540	missense	VAL,ALA	possibly-damaging	4.87		
7649	12:6078457	unknown	G/A	0	0.0227	2550	missense	PRO,LEU	probably-damaging	3.95		
7666	12:6078440	unknown	C/T	0.0116	0	2556	missense	VAL,ILE	benign	-1.9		
7673	12:6078433	unknown	G/A	0	0.0227	2558	missense	PRO,LEU	probably-damaging	4.87		1
7682	**12:6078424**	**rs35335161**	**A/T**	**4.593**	**2.3377**	**2561**	**missense**	**PHE,TYR**	**possibly-damaging**	**4.87**		**1;4**
7698	**12:6078408**	**rs16932285**	**C/T**	**0.0116**	**2.6555**	**2566**	**synonymous**	**none**	**unknown**	**4.87**		**1;4**
7707	12:6078399	rs143235468	C/T	0.0116	0.0454	2569	synonymous	none	unknown	-0.41		
7714	12:6078392	unknown	G/A	0	0.0227	2572	missense	PRO,SER	probably-damaging	4.87		
7723	12:6078383	unknown	G/A	0.0116	0	2575	missense	ARG,CYS	probably-damaging	4.77		
7724	12:6078382	unknown	C/T	0.0116	0	2575	missense	ARG,HIS	benign	-3.87		

7728	12:6078378	unknown	A/G	0.0116	0	2576	synonymous-near-splice	none	unknown	-4.04		
7732	12:6077331	unknown	G/A	0.0116	0	2578	missense	ARG,CYS	benign	4.73		
7747	12:6077316	unknown	T/G	0	0.0227	2583	missense	MET,LEU	benign	-9.47		
7761	12:6077302	unknown	A/G	0.0116	0	2587	synonymous	none	unknown	1.89		
7766	12:6077297	unknown	A/G	0.0116	0	2589	missense	ILE,THR	probably-damaging	4.73		
7773	12:6076766	unknown	G/A	0	0.0227	2591	synonymous	none	unknown	-9.72		
7774	12:6076765	rs142316324	C/T	0.0116	0.1135	2592	missense	GLY,ARG	probably-damaging	4.86		
7802	12:6076737	rs138303680	G/A	0	0.0227	2601	missense	THR,MET	benign	3.23		
7811	12:6076728	rs147052620	C/T	0	0.0227	2604	missense	ARG,HIS	benign	-10.1		
7849	12:6076690	unknown	G/A	0.0116	0	2617	synonymous	none	unknown	4.07		
7876	12:6076663	rs141666705	G/T	0	0.0454	2626	missense	PRO,THR	benign	0.75		
7940	12:6062708	rs61751302	G/A	0.1977	0.0908	2647	missense	THR,MET	benign	-3.81	Type 1	1-4;21
7987	12:6061685	unknown	G/A	0.0116	0	2663	missense-near-splice	ARG,CYS	probably-damaging	4.42		
7988	12:6061684	rs149834874	C/G	0.1977	0	2663	missense-near-splice	ARG,PRO	possibly-damaging	2.2	Type 1 (with C1130F)	8
7997	**12:6061675**	**rs78353028**	**G/A**	**0.0465**	**6.8543**	**2666**	**missense**	**THR,MET**	**benign**	**0.38**		1;3
8035	12:6061637	unknown	T/C	0	0.0454	2679	missense	ASN,ASP	benign	5.45		
8036	12:6061636	rs151129435	T/C	0.0116	0.2497	2679	missense	ASN,SER	benign	1.45		
8048	12:6061624	rs144511926	T/C	0.0116	0	2683	missense	GLU,GLY	possibly-damaging	5.45		
8079	12:6061593	rs41276732	G/A	0.2791	0.0454	2693	synonymous	none	unknown	1.54		1
8084	12:6061588	rs76459136	G/C	0.093	0	2695	missense	PRO,ARG	probably-damaging	5.45		3
8094	12:6061578	rs144030544	T/C	0.0698	0	2698	synonymous	none	unknown	-5.65		
8113	**12:6061559**	**rs7962217**	**C/T**	**5.7791**	**1.9746**	**2705**	**missense**	**GLY,ARG**	**probably-damaging**	**5.45**		1;4
8160	12:6059045	unknown	C/T	0.0116	0	2720	synonymous	none	unknown	4.71		4
8187	12:6059018	unknown	G/C	0.0116	0	2729	synonymous	none	unknown	3.58		
8273	12:6058350	rs144542595	G/A	0	0.0681	2758	missense	ALA,VAL	possibly-damaging	4.89		

8289	**12:6058334**	**rs149309674**	**G/A**	**0**	**0.4993**	**2763**	**synonymous**	**none**	**unknown**	**-1.18**		4
8324	12:6058299	unknown	G/A	0.0116	0	2775	missense	SER,PHE	benign	3.04		
8325	12:6058298	rs138588762	A/G	0.0233	0	2775	synonymous	none	unknown	-5.98		
8332	12:6058291	unknown	G/A	0.0116	0	2778	missense	ARG,TRP	probably-damaging	1.58		
8333	12:6058290	rs150577615	C/T	0.0233	0	2778	missense	ARG,GLN	benign	-2.49		
8336	12:6058287	unknown	G/A	0.0116	0	2779	missense	THR,MET	probably-damaging	1.4		
8337	12:6058286	unknown	C/T	0.0116	0	2779	synonymous	none	unknown	-6.15		1
8366	12:6058257	unknown	G/C	0.0116	0	2789	missense	THR,SER	benign	5.01		
8378	**12:6058245**	**rs143743709**	**A/G**	**0**	**0.6128**	**2793**	**missense**	**VAL,ALA**	**benign**	**5.01**		1;3
8391	12:6058232	unknown	C/T	0	0.0227	2797	synonymous	none	unknown	0.7		
8439	12:6058184	rs138263930	C/T	0	0.0227	2813	synonymous	none	unknown	3.08		

VWF gene variant data is also available online at http://evs.gs.washington.edu/EVS/. *VWF* variants previously reported are annotated with references and color coded: Orange highlighting indicates variants reported to be functional and/or associated with VWD, green highlighting indicates variants reported to be benign and/or reported in normal individuals with function unknown. Red highlighting indicates variants which introduce a premature STOP codon and predicted or known non-functional allele. The 30 missense and 28 synonymous single nucleotide variants SNV with MAF>0.1% identified by exome sequencing and successfully imputed in our African American study sample are highlighted in **bold type**.

EA, European American; AA=African American; MAF, minor allele frequency. GERP, Genomic Evolutionary Rate Profiling (GERP), which identifies functionally constrained DNA sequence elements using multiple sequence alignments to quantify nucleotide substitution deficits ("rejected substitutions") that reflect the strength of past purifying selection.

*The alleles are based on the genomic sequence (NCBI build 37) and show the reference nucleotide first and the variant or non-reference nucleotide second. Note that the VWF cDNA reference sequence (NM_000552.3) is on the reverse strand of the human genome sequence and therefore the alleles are annotated to the complementary genome build.

Reference List

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Supplemental Table 2. Functional predictions for 30 *VWF* missense variants based on sequence conservation

Chromosome: Position (NCBI Build 37)	Protein position	Amino acids	cDNA position (NM_000552.3)	Codon (NM_000552.3)	rs ID number	GERP score	SIFT score	POLYPHEN2 score	Mutation Assessor score	Condel score	Condel Prediction
12:6220051	102	Val/Met	559	Gtg/Atg	rs147514785	2.3	0	0.011	3.285	0.001	neutral
12:6219687	129	Leu/Met	640	Ctg/Atg	rs61753991	3.73	0	0.701	2.475	0.752	deleterious
12:6219681	131	Gly/Ser	646	Ggt/Agt	rs76505074	4.67	1	0	-2.695	0	neutral
12:6182828	318	Asn/Lys	1209	aaT/aaG	rs1800387	-3.54	0.01	0.005	1.34	0.004	neutral
12:6181569	346	Thr/Ile	1292	aCc/aTc	rs111971143	5.55	0.01	0.112	1.525	0.013	neutral
12:6173433	471	Val/Ile	1666	Gtc/Atc	rs1800377	-2.9	0.57	0.001	0.185	0.001	neutral
12:6172202	484	HIs/Arg	1706	cAt/cGt	rs1800378	1.25	1	0.132	-0.79	0.011	neutral
12:6153559	780	Asn/Lys	2595	aaC/aaG	rs143904314	3.27	0.07	0.999	1.54	0.499	deleterious
12:6153534	789	Thr/Ala	2620	Acc/Gcc	rs1063856	2.17	1	0	-0.895	0	neutral
12:6145649	817	His/Gln	2706	caT/caG	rs57950734	-0.03	0.02	0.998	1.69	0.857	deleterious
12:6145590	837	Ala/Asp	2765	gCc/gAc	rs75645183	3.05	0.26	0.698	1.915	0.258	neutral
12:6143913	876	Leu/Phe	2881	Ctc/Ttc	rs143762054	2.72	0.02	0.287	1.39	0.039	neutral
12:6138575	967	Gly/Asp	3155	gGc/gAc	rs141087261	3.69	0.36	0.857	1.1	0.335	neutral
12:6135091	1030	Gln/Arg	3344	cAg/cGg	rs145125264	2.27	0.01	0.055	1.415	0.007	neutral
12:6128454	1377	Ala/Val	4385	gCc/gTc	rs141211612	4.08	0	1	3.295	1	deleterious
12:6128446	1380	Ile/Val	4393	Atc/Gtc	rs11063988	-3.75	0.32	0	0.385	0.005	neutral
12:6128280	1435	Asn/Ser	4559	aAc/aGc	rs11063987	4.35	0.26	0.075	3.12	0.012	neutral
12:6128269	1439	Val/Met	4570	Gtg/Atg	rs150077670	-1.93	0.1	0.002	3.28	0.018	neutral
12:6128170	1472	Asp/His	4669	Gac/Cac	rs61750092	0.812	0.18	0	-1.085	0.011	neutral
12:6128127	1486	Ser/Leu	4712	tCg/tTg	rs149424724	3	0.27	0	1.635	0.006	neutral
12:6125820	1725	Pro/Ser	5428	Cct/Tct	rs78302129	3.39	0.1	0.172	2.515	0.034	neutral
12:6103094	2178	Ala/Ser	6787	Gcc/Tcc	rs34230288	-0.724	0.42	0	1.275	0.003	neutral
12:6103072	2185	Arg/Gln	6809	cGg/cAg	rs76342212	5.3	0.17	0.9	1.37	0.368	neutral
12:6094771	2287	Arg/Trp	7114	Cgg/Tgg	rs61750625	1.58	0	1	2.48	1	deleterious
12:6092338	2353	Glu/Asp	7314	gaG/gaT	rs112319661	0.467	0.13	0.967	1.905	0.419	neutral
12:6091089	2384	Arg/Trp	7405	Cgg/Tgg	rs145697622	4.1	0	0.998	2.35	0.974	deleterious
12:6078424	2561	Phe/Tyr	7937	tTt/tAt	rs35335161	4.87	0.16	0.395	2.135	0.059	neutral

12:6061675	2666	Thr/Met	8252	aCg/aTg	rs78353028	0.378	0.12	0.001	1.395	0.015	neutral
12:6061559	2705	Gly/Arg	8368	Gga/Cga	rs7962217	5.45	0	0.903	2.65	0.858	deleterious
12:6058245	2793	Val/Ala	8633	gTt/gCt	rs143743709	5.01	0.02	0.038	1.95	0.01	neutral

See Supplementary Methods for details.

Genomic Evolutionary Rate Profiling (GERP) identifies functionally constrained DNA sequence elements using multiple sequence alignments to quantify nucleotide substitution deficits ("rejected substitutions") that reflect the strength of past purifying selection. GERP scores ranges from -12.3 to 6.17, with 6.17 being the most conserved or functionally constrained. SIFT scores range from 0 to 1 and represent normalized probabilities for all possible substitutions based on the sequence alignment. Positions with normalized probabilities less than 0.05 are predicted to be deleterious, those greater than or equal to 0.05 are predicted to be tolerated. PolyPhen-2 range from 0 to 1 and represent the probability that the mutation is damaging. A mutation is also appraised qualitatively, as benign, possibly damaging, or probably damaging based on optimized false positive rate (FPR) thresholds. Mutations with their posterior probability scores associated with estimated FPR at or below 5% are predicted to be probably damaging (more confident prediction). Mutations with the posterior probabilities associated with FPR at or below the 10% are predicted to be possibly damaging (less confident prediction). Mutations with estimated FPR above 10% are classified as benign. MutationAssessor provides a functional impact score that ranges from -5.76 to +5.37 and variants scoring below 1.938 are classified as non-functional and variants scoring above this threshold are predicted to result in altered function. Condel (CONsensus DELeteriousness score of non-synonymous single nucleotide variants) integrates the output of SIFT, Polyphen2, and MutationAssessor into a single consensus prediction.

Supplemental Table 3. Association of 30 *VWF* missense variants with natural-log transformed von Willebrand factor antigen (VWF) and factor VIII activity (FVIII)

						Natural-log transformed VWF:Ag					Natural-log transformed FVIII:C				
Chromosome: Position (NCBI Build 37)	Rs #	Alleles (NCBI Build 37)*	Amino acids	MAF	Imputation Rsq	Beta coefficient	SE	*P* -value	*P* hetero-geneity	I^2 metric	Beta coefficient	SE	*P* -value	*P* hetero-geneity	I^2 metric
12:6220051	147514785	C/T	Val102Met	0.006	0.877	0.142	0.084	0.092	0.51	0	0.1423	0.052	0.0063	0.83	0
12:6219687	61753991	G/T	Leu129Met	0.009	0.775	0.025	0.068	0.706	0.33	12.3	0.0909	0.047	0.053	0.07	54.4
12:6219681	76505074	C/T	Gly131Ser	0.02	0.748	-0.082	0.041	0.046	0.12	44.3	-0.0901	0.03	0.003317	0.75	0
12:6182828	1800387	A/T	Asn318Lys	0.41	0.794	0.026	0.012	0.028	0.42	0	0.0092	0.008	0.295	0.78	0
12:6181569	111971143	A/G	Thr346Ile	0.013	0.824	0.044	0.052	0.397	0.59	0	0.0266	0.035	0.455	0.96	0
12:6173433	1800377	C/T	Val471Ile	0.15	0.744	0.015	0.017	0.38	0.64	0	-0.0091	0.012	0.475	0.83	0
12:6172202	1800378	C/T	His484Arg	0.22	0.762	-0.023	0.014	0.109	0.02	65	-0.0042	0.01	0.694	0.98	0
12:6153559	143904314	C/G	Asn780Lys	0.0035	0.968	0.188	0.103	0.0693	0.44	0	0.093	0.073	0.198	0.31	15.5
12:6153534	1063856	C/T	Thr789Ala	0.41	0.996	-0.066	0.01	1.05E-09	0.18	35.6	-0.037	0.007	1.24E-06	0.07	53.3
12:6145649	57950734	A/T	His817Gln	0.11	0.966	0.031	0.018	0.0776	0.23	28.6	0.1205	0.012	1.77E-21	0.01	68.2
12:6145590	75645183	G/T	Ala837Asp	0.024	0.762	0.081	0.038	0.0341	0.43	0	0.012	0.028	0.673	0.9	0
12:6143913	143762054	A/G	Leu876Phe	0.0012	0.87	-0.013	0.009	0.164	0.32	10.7	0.325	0.17	0.056	0.42	0
12:6138575	141087261	C/T	Gly967Asp	0.027	0.816	0.02	0.036	0.578	0.82	0	0.0263	0.026	0.311	0.27	23.4
12:6135091	145125264	C/T	Gln1030Arg	0.008	0.903	0.0133	0.009	0.158	0.59	0	0.0004	0.008	0.963	0.74	0
12:6128454	141211612	A/G	Ala1377Val	0.0023	0.809	-0.335	0.132	0.0114	0.05	61.6	-0.149	0.088	0.09	0.37	5.4
12:6128446	11063988	C/T	Ile1380Val	0.11	0.831	-0.059	0.018	0.0016	0.78	0	-0.064	0.013	2.74E-06	0.33	12.9
12:6128280	11063987	C/T	Asn1435Ser	0.11	0.854	-0.055	0.018	0.0028	0.8	0	-0.064	0.013	1.71E-06	0.3	18
12:6128269	150077670	C/T	Val1439Met	0.0046	0.901	-0.327	0.095	0.0006	0.27	21.9	-0.118	0.066	0.074	0.69	0
12:6128170	1800383	C/G	Asp1472His	0.4	0.72	0.038	0.012	0.001	0.48	0	0.0183	0.009	0.055	0.17	37.6
12:6128127	149424724	A/G	Ser1486Leu	0.008	0.751	-0.358	0.067	1.18E-07	0.11	45.8	-0.12	0.049	0.015	0.17	37.4
12:6125820	78302129	A/G	Pro1725Ser	0.024	0.713	0.097	0.039	0.012	0.33	12.5	0.012	0.029	0.666	0.95	0
12:6103094	34230288	A/C	Ala2178Ser	0.0038	0.781	-0.057	0.115	0.617	0.18	38.6	-0.1	0.082	0.223	0.22	31.4
12:6103072	76342212	C/T	Arg2185Gln	0.2	0.969	-0.101	0.014	6.24E-13	0.57	0	-0.085	0.01	1.86E-17	0.08	52.1
12:6094771	61750625	A/G	Arg2287Trp	0.01	0.685	-0.306	0.063	1.33E-06	0.06	55.7	-0.11	0.048	0.021	0.11	46.8

12:6092338	112319661	C/G	Glu2353Asp	0.0066	0.947	0.012	0.009	0.191	0.03	65.5	0.003	0.008	0.717	0.01	71.6
12:6091089	145697622	A/G	Arg2384Trp	0.0023	0.866	-0.241	0.154	0.118	0.17	37	-0.027	0.075	0.721	0.34	11.5
12:6078424	35335161	A/T	Phe2561Tyr	0.025	0.595	0.007	0.043	0.866	0.72	0	0.008	0.031	0.777	0.14	41.6
12:6061675	78353028	A/G	Thr2666Met	0.07	0.985	0.038	0.021	0.078	0.36	7.7	0.037	0.015	0.014	0.18	36.3
12:6061559	7962217	C/T	Gly2705Arg	0.02	0.999	0.023	0.039	0.549	0.92	0	0.033	0.029	0.254	0.53	0
12:6058245	143743709	A/G	Val2793Ala	0.007	0.902	0.154	0.077	0.046	0.08	52.2	0.027	0.049	0.578	0.09	49.6

MAF, minor allele frequency; SE, standard error; VWF:Ag, von Willebrand factor antigen; FVIII:C, factor VIII clotting activity.

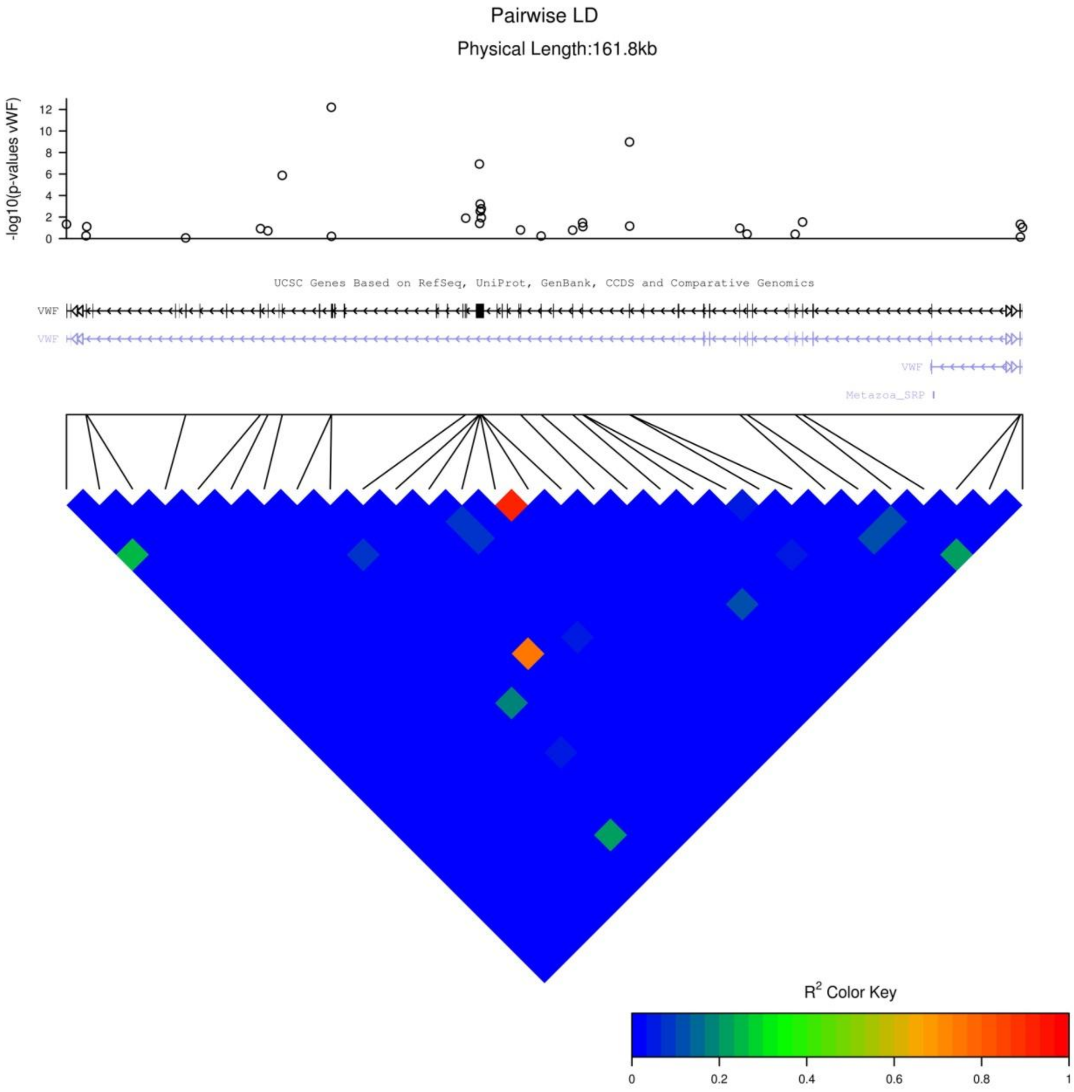
*The alleles are based on the genomic sequence (NCBI build 37) and show the reference nucleotide first and the variant or non-reference nucleotide second. Note that the VWF cDNA reference sequence (NM_000552.3) is on the reverse strand of the human genome sequence and therefore the alleles are annotated to the complementary genome build.

As described under Supplemental Methods, we tested for between-study heterogeneity of results by using Cochran's *Q* statistic (*P* for heterogeneity) and the I^2 inconsistency metric. The I^2 metric ranges from 0-100%, and measures the degree of inconsistency across studies in a meta-analysis as the percentage of total variation across studies that is due to heterogeneity rather than chance. Low, moderate, and high degrees of heterogeneity between studies is defined as I^2 values of 25%, 50%, and 75%, respectively.

Supplemental Table 4. *VWF* missense variants located in A1 domain and their association with natural-log transformed VWF antigen and VWF ristocetin cofactor activity

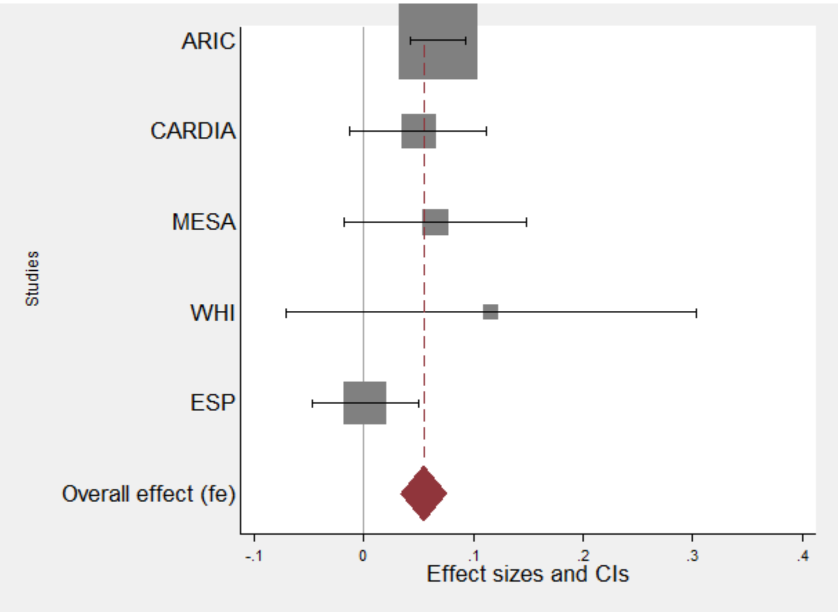
Variant	Rs#	annotation	N	VWF antigen Beta	VWF antigen SE	VWF antigen P-value	N	VWF activity Beta	VWF activity SE	VWF activity P-value	N	VWF activity/antigen ratio Beta	VWF activity/antigen ratio SE	VWF activity/antigen ratio P-value
12:6128446	11063988	Ile1380Val	242	0.080	0.069	0.25	172	0.055	0.080	0.49	166	-0.0004	0.013	0.97
12:6128280	11063987	Asn1435Ser	242	0.080	0.069	0.25	172	0.053	0.080	0.50	166	-0.0005	0.013	0.97
12:6128269	150077670	Met1439Val	242	-0.52	0.25	0.037	172	-0.55	0.24	0.024	166	-0.0067	0.037	0.85
12:6128170	11063988	Asp1472His	242	0.082	0.048	0.089	172	0.123	0.053	0.022	166	-0.0086	0.008	0.30
12:6128127	149424724	Ser1486Leu	242	-0.63	0.39	0.11	172	-0.51	0.45	0.27	166	0.051	0.068	0.46

Supplemental Figure 1: Pairwise linkage disequilibrium (r-squared) between 30 VWF missense variants in African Americans. The upper panel shows the -log(P-value) for association for each variant with VWF levels. Shown is the region on chromosome 12p13.31 containing *VWF* (nucleotides 6,058,040 - 6,233,836 corresponding to NC_000012.11). The bottom panel is a heat map representing strength of LD between variants. Overall, there is little LD between VWF missense variants in AA. Only two pairs of variants had r^2 >0.5: 12:6128280 (Ser1435Asn) with 12:6128446 (Ile1380Val) (r2=0.89; red) and 12:6145590 (Asp837Ala) with 12:6125820 (Ser1725Pro) (r2=0.73; orange).

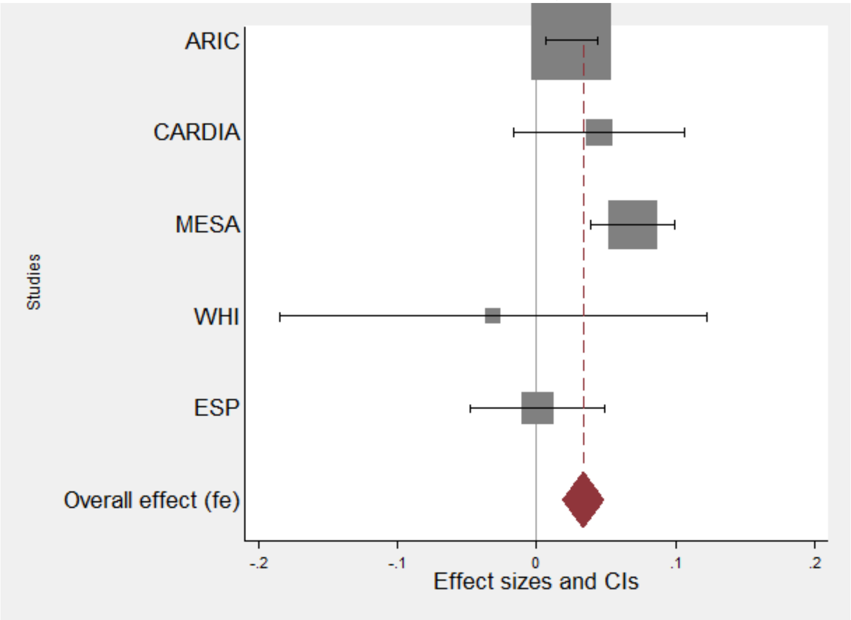


Supplemental Figure 2: Forest plots of individual study and meta-analysis results for nine VWF missense variants.

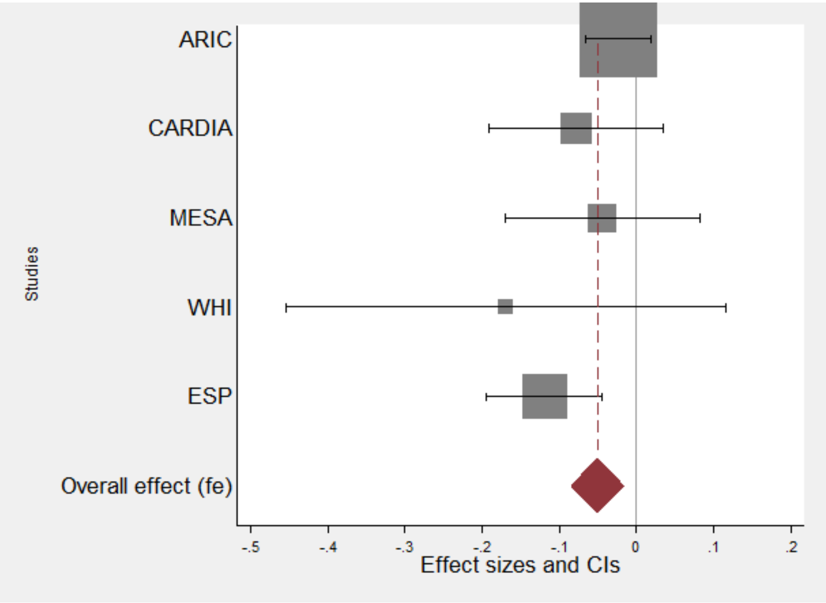
ln(VWF) and p.Thr789Ala



ln(FVIII) and p.Thr789Ala



ln(VWF) and p.His817Gln



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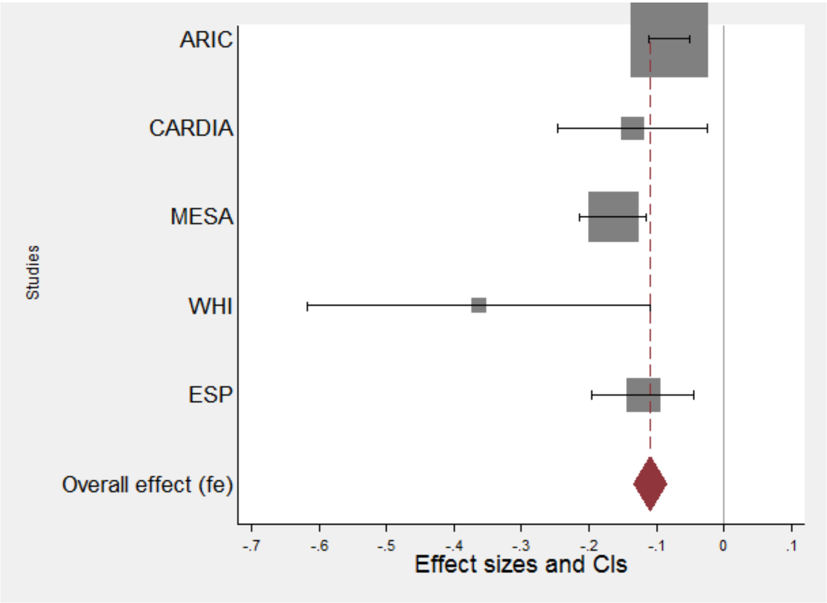

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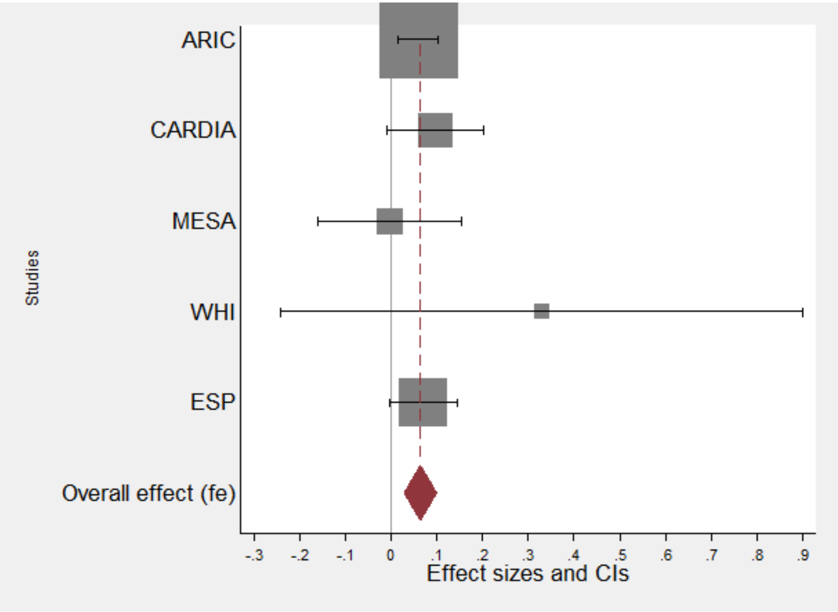

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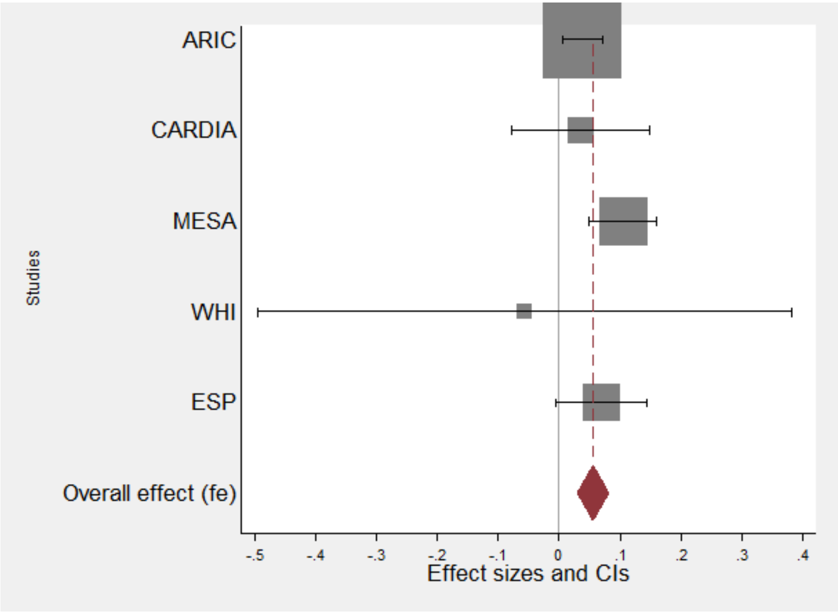
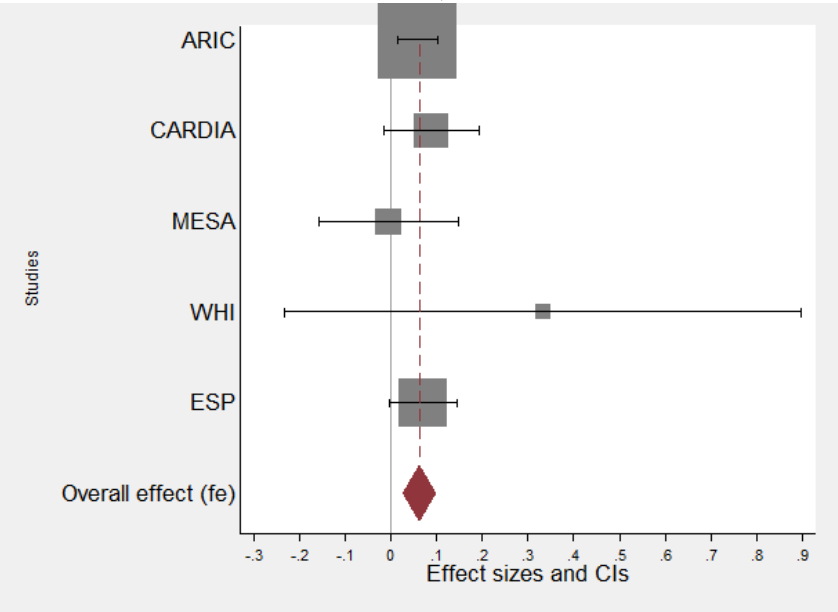


ln(VWF) and p.Asn1435Ser



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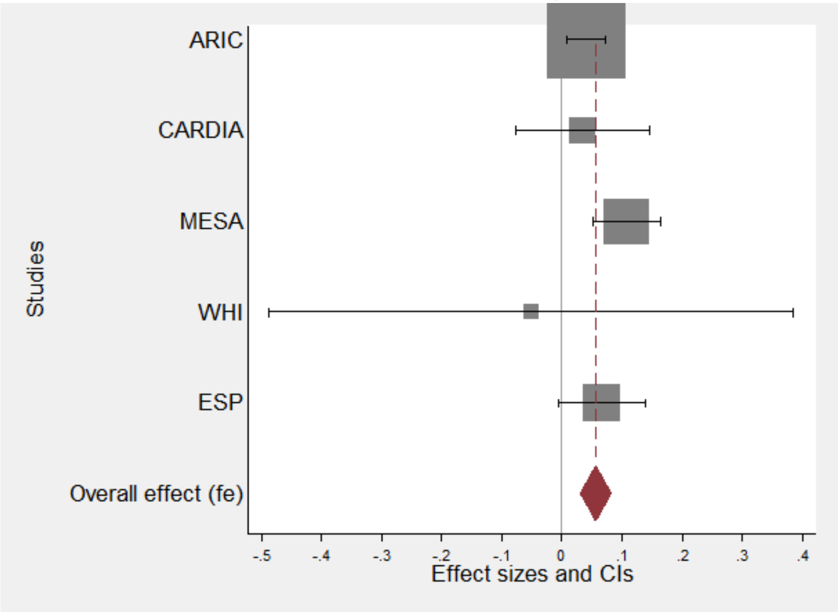

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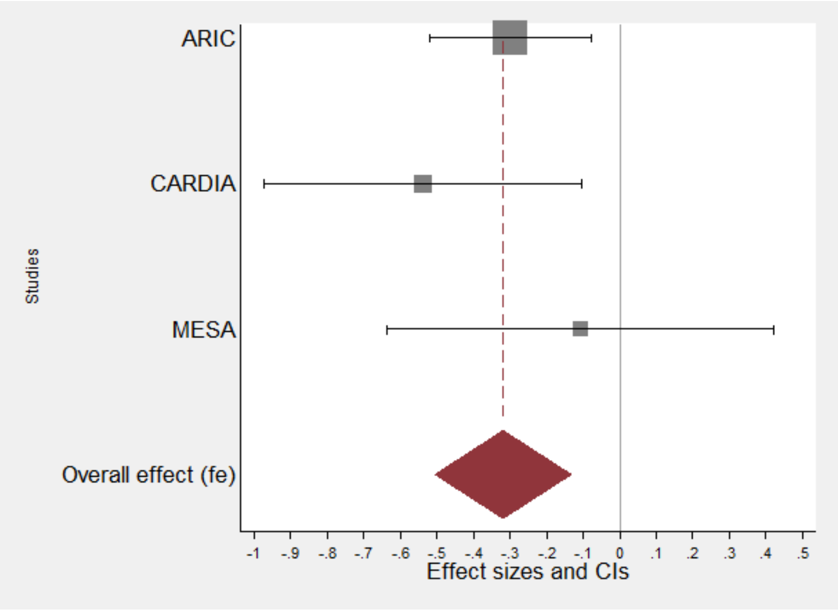

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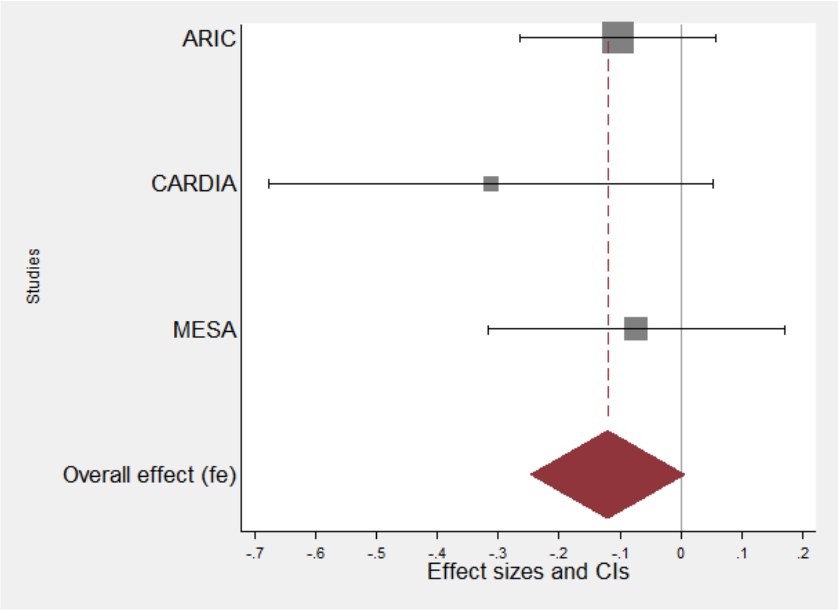

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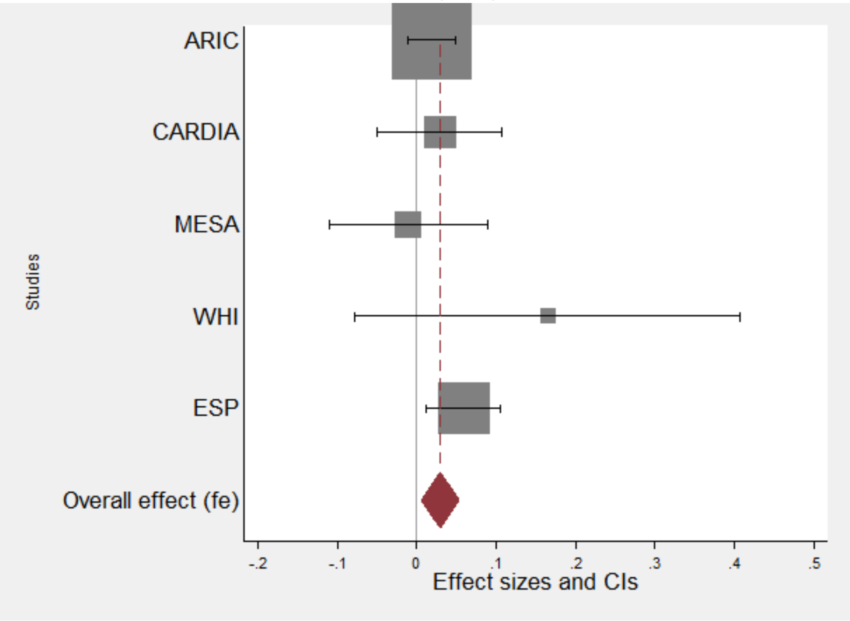

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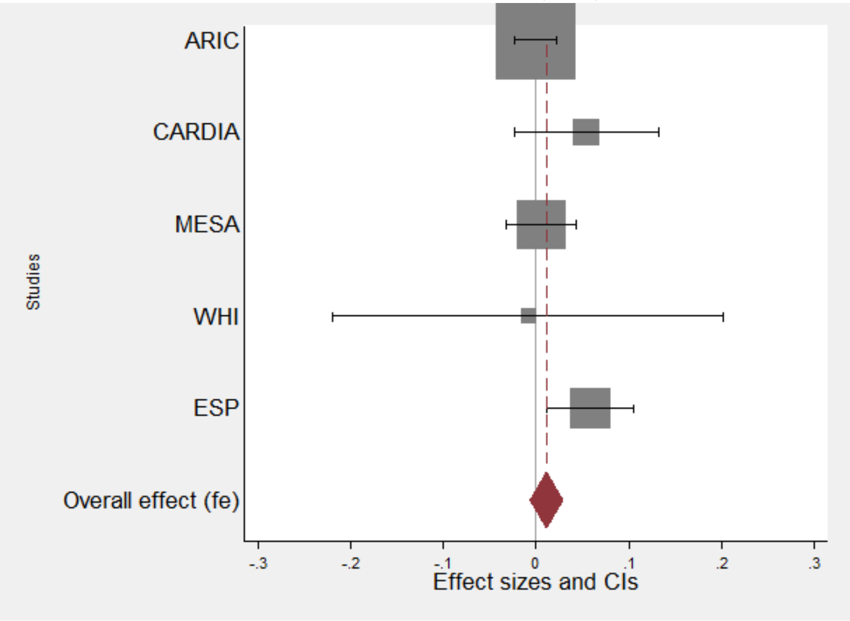
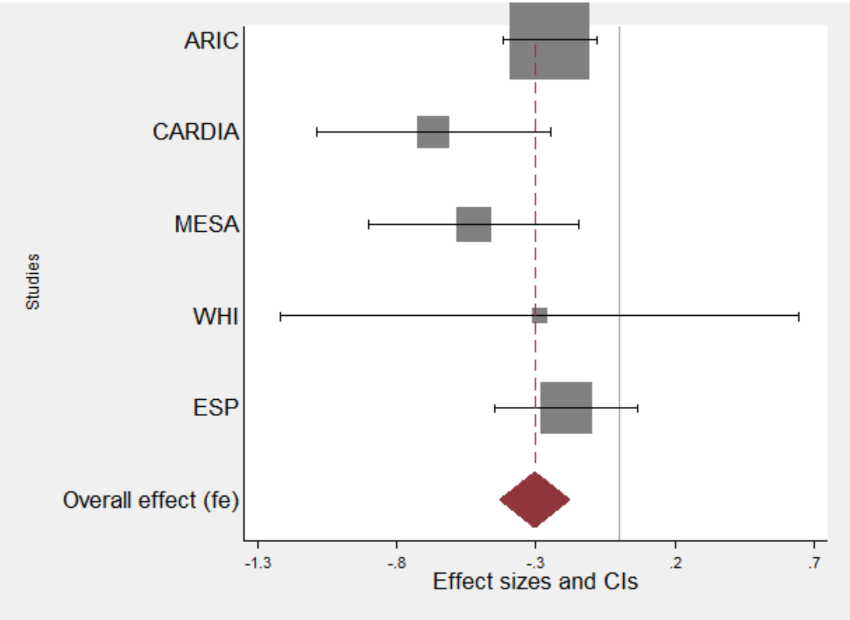
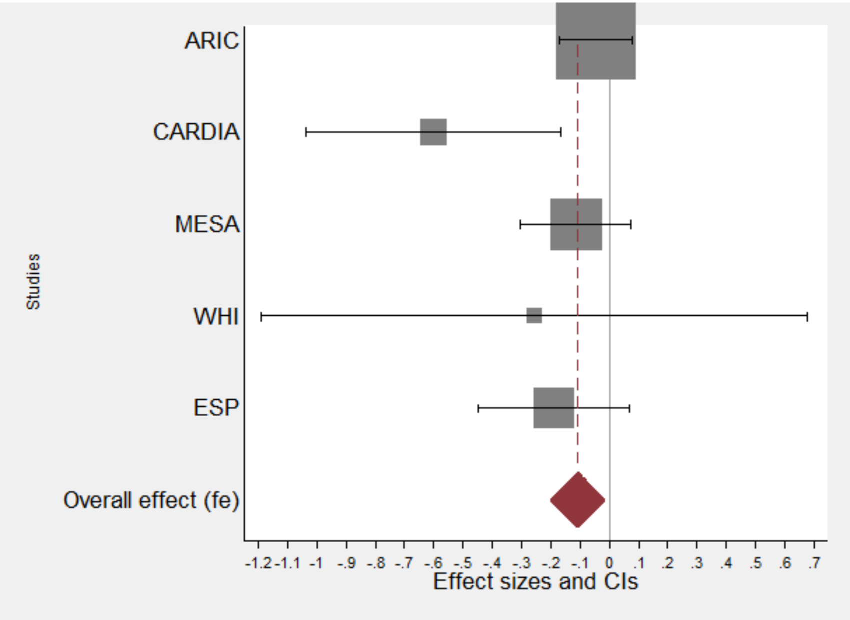


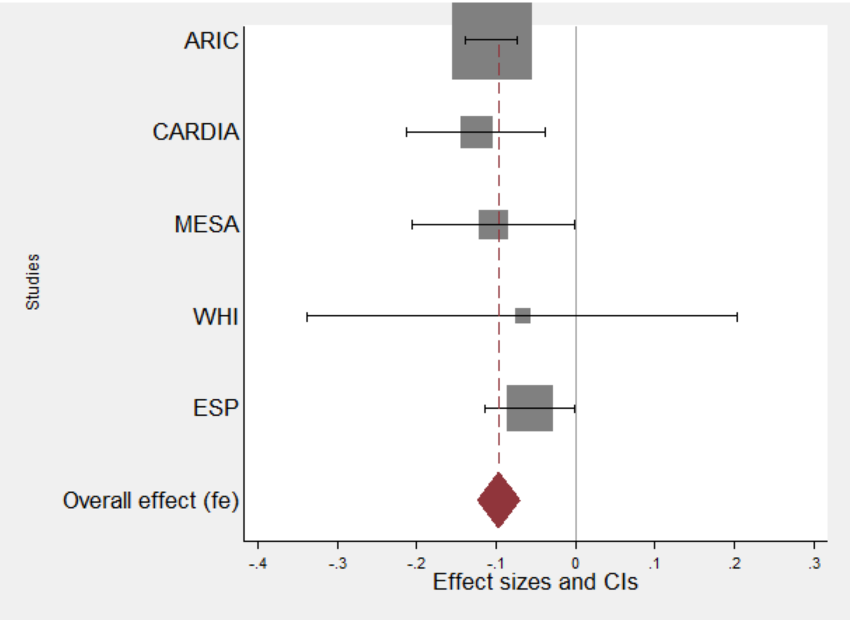
ln(VWF) and p.Ser1486Leu



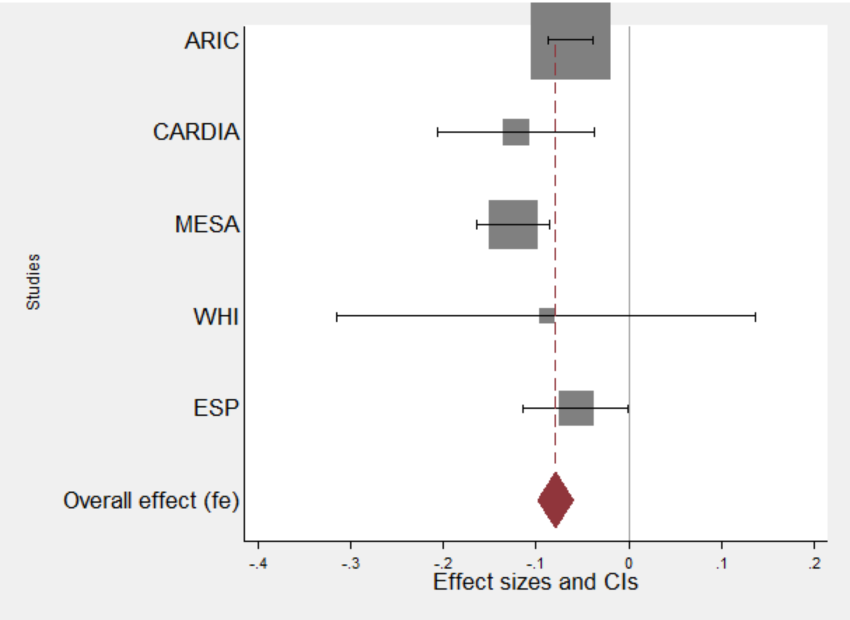
ln(FVIII) and p.Ser1486Leu

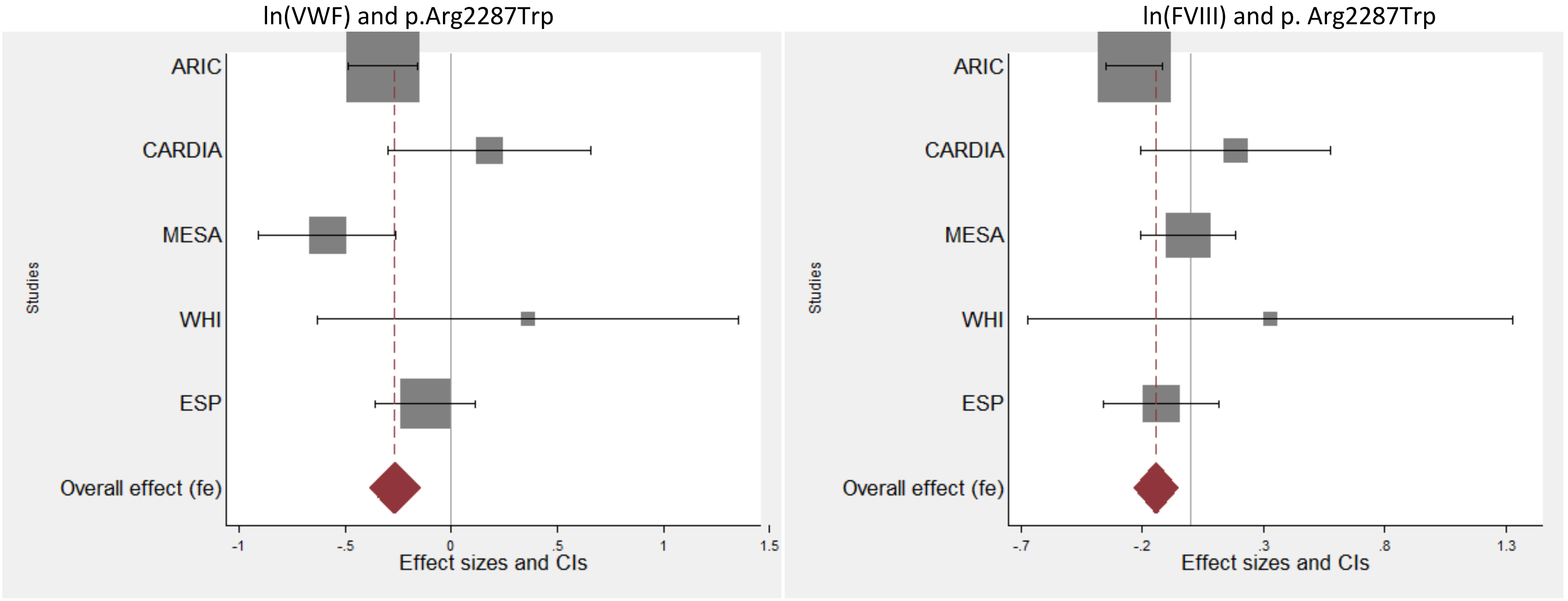


ln(VWF) and p.Arg2185Gln



ln(FVIII) and p. Arg2185Gln




ln(VWF) and p.Arg2287Trp

ln(FVIII) and p. Arg2287Trp

The left-hand column or Y-axis lists the names of the individual studies. The right-hand column is a plot of the measure of effect (on a natural logarithmic scale) for each of these studies (represented by a square) incorporating confidence intervals (CI) represented by horizontal lines. The area of each square is proportional to the study's weight in the meta-analysis. The overall meta-analysis measure of effect is represented as a dashed vertical red line. This summary measure of effect is plotted as a diamond, the lateral points of which indicate confidence intervals for this estimate. A vertical line representing no effect is also plotted in light grey.