Ethnicity and Haemostasis: Challenge in the genomics era

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Factor VIII (FVIII) and its carrier protein von Willebrand factor (VWF) regulate haemostasis and thrombosis. Higher plasma levels of these factors have been associated with risk of arterial and venous thrombosis (VT) [1,2]. The causal relation between thrombotic risk and increased FVIII levels has been a topic of intense debate. Indeed, as FVIII is an acute phase reactant, it could be only a marker of the inflammatory process, which is known to play a major role in cardiovascular disease. However, Jick et al in 1969[3] and Medalie et al in 1971[4] reported that non-O blood group was associated with increased risk of VT and coronary disease respectively. This association of ABO blood group with VT was later found to be largely explained by plasma FVIII levels[5,6]. Recent data obtained using Mendelian randomization analyses formally suggest that high FVIII levels are causally linked to VT and coronary artery disease risk[7].

Cardiovascular diseases vary across populations and several evidences are in favor of an increased risk in African Americans[8]. African Americans have the highest levels of FVIII and VWF among all ethnic groups studied[9]. In addition, markers of activation of the coagulation system such as plasma D-dimers are higher in African Americans[10]. Whether these findings represent an underlying genetic defect or are simply markers of increased coagulation due to another cause is unknown.

One article published in this issue of *JTH* address the question of the association between high factor VIII levels with incident cardiovascular disease specifically in African Americans using the community-based Jackson Heart Study[11]. This study shows a significant linear increase of incident heart failure (HF) and mortality. This association was still present in the fully adjusted models (including CRP as a marker of inflammation). Significant associations were not observed for stroke and overall coronary heart disease (CHD). The association between FVIII levels and HF and mortality which remains after adjustment may suggest a genetic effect. Several genetic variants associated with FVIII levels have been recently

identified by GWAS approaches[7]. However, until now most GWAS have been performed in individuals of European ancestry where it is known that linkage disequilibrium can extend over large genomic regions compared to other populations, including Africans. Moreover, as underlined by the authors, African population-specific variants are poorly represented on genotyping arrays and current imputation reference panels. To circumvent this bias, the authors of the present study have used whole genome sequencing data (which is now possible in large sets of unrelated individuals) obtained through the TOPMed project. They showed that the ABO blood group was, as expected, responsible for the most important part of the heritability of FVIIII levels. ABO blood group is known to be the only common genetic factor robustly associated with CHD, stroke and VT [12–14]. This study was the first to identify a second signal at the VWF locus highly specific to African Americans. The most likely causal variant is the rs57950734 which encodes p.His817Gln located within the VWF D' domain within the FVIII binding region. This variant which has been reported in several patients with type 2N von Willebrand disease result in significantly lower FVIII binding capacity[15]. The higher prevalence among African than non-African populations confirms the need to specifically analyze genetic determinants in different ethnicities. They find no evidence of association between VWF rs115708869 and incident HF or mortality in JHS, but this analysis is limited due the relatively small number cases.

Not all the missing heritability is hiding in genetic variations. Epigenetic mechanisms are also proposed as a possible source that could contribute to this heritability. The expression of several genes encoding haemostatic proteins, including FVIII, has been shown to be subjected to DNA methylation mechanisms[16]. Specific high throughput technologies are now available to quantify methylation profiles from cells, tissues and blood from large cohorts of subjects. This has been done in the present study leading to the identification of a number of methylation marks particularly at the ABO locus which is associated with FVIII levels.

However, a primary concern in this new era of epigenetic epidemiology is the tissue-specific nature of the epigenome. Indeed, while assessment of DNA methylation in whole blood has been shown able to identify robust and biologically relevant epigenetic variation related to cardiometabolic quantitative risk factors[17,18], it remains to be determined whether it can be relevant for FVIII which is produced in endothelial cells.

In conclusion, thoroughly designed epidemiological research (including GWAS) should be expanded to non-white populations with higher genetic diversity to facilitate the identification of additional genetic risk factors for cardiovascular disease. This has been an ongoing challenge in the genomics era in which most studies involve predominantly white, European cohorts.

References

1 Rietveld IM, Lijfering WM, le Cessie S, Bos MHA, Rosendaal FR, Reitsma PH, Cannegieter SC. High levels of coagulation factors and venous thrombosis risk: strongest association for factor VIII and von Willebrand factor. *J Thromb Haemost* 2019; **17**: 99–109.

2 Smith A, Patterson C, Yarnell J, Rumley A, Ben-Shlomo Y, Lowe G. Which hemostatic markers add to the predictive value of conventional risk factors for coronary heart disease and ischemic stroke? The Caerphilly Study. *Circulation* 2005; **112**: 3080–7.

3 Jick H, Slone D, Westerholm B, Inman WH, Vessey MP, Shapiro S, Lewis GP, Worcester J. Venous thromboembolic disease and ABO blood type. A cooperative study. *Lancet* 1969; **1**: 539–42.

4 Medalie JH, Levene C, Papier C, Goldbourt U, Dreyfuss F, Oron D, Neufeld H, Riss E. Blood groups, myocardial infarction and angina pectoris among 10,000 adult males. *N Engl J Med* 1971; **285**: 1348–53.

5 Koster T, Blann AD, Briët E, Vandenbroucke JP, Rosendaal FR. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. *Lancet* 1995; **345**: 152–5.

6 le Cessie S, Debeij J, Rosendaal FR, Cannegieter SC, Vandenbroucke JP. Quantification of bias in direct effects estimates due to different types of measurement error in the mediator. *Epidemiology* 2012; **23**: 551–60.

7 Lindström S, Wang L, Smith EN, Gordon W, van Hylckama Vlieg A, de Andrade M, Brody JA, Pattee JW, Haessler J, Brumpton BM, Chasman DI, Suchon P, Chen M-H, Turman C, Germain M, Wiggins KL, MacDonald J, Braekkan SK, Armasu SM, Pankratz N, et al. Genomic and transcriptomic association studies identify 16 novel susceptibility loci for venous thromboembolism. *Blood* 2019; **134**: 1645–57.

8 Carnethon MR, Pu J, Howard G, Albert MA, Anderson CAM, Bertoni AG, Mujahid MS, Palaniappan L, Taylor HA, Willis M, Yancy CW, American Heart Association Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; and Stroke Council. Cardiovascular Health in African Americans: A Scientific Statement From the American Heart Association. *Circulation* 2017; **136**: e393–423.

9 Lutsey PL, Cushman M, Steffen LM, Green D, Barr RG, Herrington D, Ouyang P, Folsom AR. Plasma hemostatic factors and endothelial markers in four racial/ethnic groups: the MESA study. *J Thromb Haemost* 2006; **4**: 2629–35.

10 Khaleghi M, Saleem U, McBane RD, Mosley TH, Kullo IJ. African-American ethnicity is associated with higher plasma levels of D-dimer in adults with hypertension. *J Thromb Haemost* 2009; **7**: 34–40.

11 Raffield LM, Lu AT, Szeto MD, Little A, Grinde KE, Shaw J, Auer PL, Cushman M, Horvath S, Irvin MR, Lange EM, Lange LA, Nickerson DA, Thornton TA, Wilson JG, Wheeler MM, NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium, TOPMed Hematology & Hemostasis Working Group, Zakai NA, Reiner AP. Coagulation factor VIII: Relationship to cardiovascular disease risk and whole genome sequence and epigenome-wide analysis in African Americans. *J Thromb Haemost* 2020.

12 Nikpay M, Goel A, Won H-H, Hall LM, Willenborg C, Kanoni S, Saleheen D, Kyriakou T, Nelson CP, Hopewell JC, Webb TR, Zeng L, Dehghan A, Alver M, Armasu SM, Auro K, Bjonnes A, Chasman DI, Chen S, Ford I, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet* 2015; **47**: 1121–30.

13 Trégouët D-A, Heath S, Saut N, Biron-Andreani C, Schved J-F, Pernod G, Galan P, Drouet L, Zelenika D, Juhan-Vague I, Alessi M-C, Tiret L, Lathrop M, Emmerich J, Morange P-E. Common susceptibility alleles are unlikely to contribute as strongly as the FV and ABO loci to VTE risk: results from a GWAS approach. *Blood* 2009; **113**: 5298–303.

14 Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, Rutten-Jacobs L, Giese A-K, van der Laan SW, Gretarsdottir S, Anderson CD, Chong M, Adams HHH, Ago T, Almgren P, Amouyel P, Ay H, Bartz TM, Benavente OR, Bevan S, et al. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet* 2018; **50**: 524–37.

15 Kroner PA, Foster PA, Fahs SA, Montgomery RR. The defective interaction between von Willebrand factor and factor VIII in a patient with type 1 von Willebrand disease is caused by substitution of Arg19 and His54 in mature von Willebrand factor. *Blood* 1996; **87**: 1013–21.

16 El-Maarri O, Becker T, Junen J, Manzoor SS, Diaz-Lacava A, Schwaab R, Wienker T, Oldenburg J. Gender specific differences in levels of DNA methylation at selected loci from human total blood: a tendency toward higher methylation levels in males. *Hum Genet* 2007; **122**: 505–14.

17 Monte E, Vondriska TM. Epigenomes: the missing heritability in human cardiovascular disease? *Proteomics Clin Appl* 2014; **8**: 480–7.

18 Dick KJ, Nelson CP, Tsaprouni L, Sandling JK, Aïssi D, Wahl S, Meduri E, Morange P-E, Gagnon F, Grallert H, Waldenberger M, Peters A, Erdmann J, Hengstenberg C, Cambien F, Goodall AH, Ouwehand WH, Schunkert H, Thompson JR, Spector TD, et al. DNA methylation and body-mass index: a genome-wide analysis. *Lancet* 2014; **383**: 1990–8.