African and African-American Contribution to the Knowledge of the FVII Padua (Arg304Gln) Defect

Conflict of interest: The authors declare that they have no conflict of interest.

https://doi.org/10.1016/j.jnma.2019.08.004

Dear Madams and Sirs,

Factor VII Padua is a peculiar FVII defect characterized by discrepant levels of FVII activity depending on the thromboplastin used in the assay system. Factor VII activity levels are low, less than 5% of normal, when a rabbit brain thromboplastin is used but are normal if one uses an ox Brain reagent. Intermediate or low-normal levels are obtained with thromboplastins of human origin or recombinant reagents. The defect was first seen in Padua in 1978.[1] Other cases were then reported in several areas of the world.[2] In 1991 it was demonstrated that the defect was due to an Arg304Gln mutation in exon 8.[3,4] The defect is mainly concentrated in the Mediterranean basin and in the USA.[5–7] Strict migratory patterns occurred between Mediterranean countries and North America. However, these migratory patterns failed to explain the fact that all homozygous patients seen in the USA are African- Americans.[5–12] Sufficient data are now available to allow a plausible explanation for this observation. "Forced" emigration from West Africa countries has to be incriminated.[13,14] Taking into account the pattern of this "forced" emigration, it may be concluded that the West Africa countries are the origin of the cases seen in the USA, as a result of the tragic, "forced" emigration carried out by slave traders during about three centuries.[15,16]

The above mentioned assumption is based on the following facts.

1) Heterozygotes for the mutation have been found in West Africa countries in about 1.8% of subjects.[13,14]
2) The percentage seems is even higher (2.5%) among African-Americans. However this calculation was obtained by a very small population sample and therefore has only a limited value.[13,14]
3) All homozygotes found in the USA are African Americans.[5–12]
4) Intracial marriages or matings were frequent among African-American and this explain the appearance of homozygotes. Does the mutation have a phylogenetic significance. This is still unknown, however, since these patients have little or no bleeding tendency the mutation could be envisaged as a defense against other mutations which are associated with bleeding.

Another interesting question regards the possible link between the West Africa countries and the southern Mediterranean countries. No study is available, however it cannot be completely excluded despite the geographical barrier represented by the Sahara Desert. Cases of homozygous FVII Padua have been described in northern African States (Tunisia).[17]

The mechanism underlying this lack of bleeding is connected with the normal FVII antigen present in these patients. The mutation is actually a special Type 2 defect with variable decrease of FVII activity but normal FVII antigen or protein.

The recent findings of heterozygotes for this mutation in the population of West Africa countries and, in a more significant number, among the African −Americans, together with the observation that all proven or highly probable homozygotes seen in the USA are of African descent, clearly established the link between the two geographical areas. Because of the above a link between the Mediterranean countries and the USA has to be excluded. Nobody has emphasized so far the contribution of Africans to the understanding of this peculiar FVII defect. We are happy to have such opportunity. We hope this note will spur the interest in this clotting disorder. No epidemiological study or population survey has ever been carried out so far in the USA. All papers published on the subject limited themselves to the description of the patients. Since the defect in fact is associated with an increased risk of venous thrombosis,[18] it would be important, to find if it plays a role in the pathogenesis of venous thrombosis among African Americans.

Furthermore, since these patients rarely show a bleeding tendency it is important, in case of surgical procedures, to use replacement therapy with extreme caution in order to avoid the triggering of thrombotic complications.[19]

A diagnostic difficulty has to be overcome. Since these patients show no bleeding tendency, clinical observation rarely brings to the correct diagnosis.

The widespread introduction of human placenta derived or human recombinant thromboplastins which yield even in homozygotes near normal or only a mild defect often prevents a correct diagnosis. Furthermore, these tests are normal in the heterozygotes. A diagnosis can be reached only by using rabbit brain derived reagents which yield low FVII levels.[20] Needless to say that the diagnosis has to be confirmed by genetic studies.

Antonio Girolami, M.D.*, Silvia Ferrari, Ph.D.,
Elisabetta Cosi, M.D.
University of Padua Medical School, Department of Medicine, Padua, Italy
E-mail: antonio.girolami@unipd.it

REFERENCES

1. Girolami, A., Fabris, F., Dal Bo Zanon, R., Ghiotto, G., & Burul, A. (1978). Factor VII Padua: a congenital coagulation disorder due to an abnormal factor VII with a peculiar activation pattern. *J Lab Clin Med, 91*, 387–395.
2. Girolami, A., Berti de Marinis, G., Bonamigo, E., & Allemand. (2011). Worldwide diffusion of FVII Arg304Gln coagulation defect (FVII Padua). *Eur J Haematol, 86*, 135–139.
3. James, H. L., Kumar, A., Girolami, A., Hubbard, J., & Fair, D. (1991). Variant coagulation Factor X and VII with point mutations in a highly conserved motif in the substrate binding pocket, comparative molecular modelling. *Thromb Haemost, 69*(Suppl), 937 (Abstract).
4. O'Brien, D. P., Gale, K. M., Anderson, J. S., et al. (1991). Purification and characterization of factor VII 304-Gln: a variant molecule with reduced activity isolated from a clinically unaffected male. *Blood, 78*, 132–140.
5. Triplett, D. A., Brandt, J. T., Batard, M. A., Schaffer Dixon, J. L., & Fair, D. S. (1985). Hereditary factor VII deficiency: heterogeneity defined by combined functional and immunochemical analysis. *Blood, 66*, 1284–1287.
6. Pollak, E. S., Russell, T. T., Ptashkin, B., Smith-Whitley, K., Camire, R. M., & Bauer, K. A. (2006). Asymptomatic factor VII deficiency in African Americans. *Am J Clin Pathol, 126*, 128–132.
7. Kirkel, D., Lin, T. W., Fu, S. W., et al. (2010). Asymptomatic factor VII deficiency: gene analysis and structure-function relationships. *Blood Coagul Fibrinolysis, 21*, 91–94.
8. Sabharwal, A. K., Kuppuswamy, M. N., Foster, D. C., et al. (1992). Factor VII deficiency (FVII Richmond , R304Q Mutant) associated with thrombosis. *Circulation, 86*(Suppl), 679 (Abstract).
9. Shurafa, M. S., Kumar, A., Fair, D. S., & James, H. L. (1993). The molecular defect in factor VII Detroit is due to substitution of Arg (304) by Glu. *FASEB J, 7*, 115 (Abstract).
10. Krauss, J. S., Matthews, A., Oliver, J., Lightsey, A., Jonah, M. H., & Pantazis, C. G. (1994). African-American factor VII-deficient variants in Georgia (FVII variants). *Am J Hematol, 47*, 239–241.
11. Kuppuswamy, M., Sahbarwal, A., Birktoff, J., & Bajay, S. (1993). Molecular characterization of human factor-VII Kansas (gk704)-substitution of Gln100 by Arg in one allele and of Arg304 by Gln possibly in the other allele. *Thromb Haemost, 69*, 1291 (Abstract).
12. Barnett, J. M., Demel, K. C., Mega, A. E., Butera, J. N., & Sweeney, J. D. (2005). Lack of bleeding in patients with severe factor VII deficiency. *Am J Hematol, 78*, 134–137.
13. About 1000 Genomes http://www.internationalgenome.org/about.
14. Auton, A., & Abecasis, G. (2015). A global reference for human genetic variation. The 1000 Genomes Project Consortium. *Nature, 526*, 68–87.
15. *World Book Encyclopedia*. Slavery Vol.17, Pag.415; Vol. 14, Pag. 106. (1972). Chicago: Field Educat. Corp.
16. Enciclopedia Britannica. (1963). *Slavery* (vol. 20, 703–782). Chicago: William Barstant, Pub.
17. Fromovich-Amit, Y., Zivelin, A., Rosenberg, N., Landau, M., Rosa, J. P., & Seligsohn, U. (2005). Of four mutations in the factor VII gene in Tunisian patients, one novel mutation (Ser339Phe) in three unrelated families abrogates factor X activation. *Blood Coagul Fibrinolysis, 16*, 369–374.
18. Girolami, A., Cosi, E., Ferrari, S., Girolami, B., & Randi, M. L. (2019). Thrombotic events in homozygotes with a proven or highly probable Arg304Gln Factor VII mutation (FVII Padua): only limited replacement therapy is needed in case of surgery. *Card Haem Disord Drug Targ*, 2019; http://doi.org/10.2174/1871529X19666190308114842.
19. Girolami, A., Bertozzi, I., Rigoni, I., Enciclopedia, B., SlaveryMuzzolon, R., & Vettore, S. (2011). Congenital FVII deficiency and thrombotic events after replacement therapy. *J Thromb Thrombolysis, 32*, 362–367.
20. Girolami, A., Berti de Marinis, G., Bonamigo, E., Sartori, R., & Vettore, S. (2010). Ox brain versus rabbit brain thromboplastin assays are the best tool for a preliminary diagnosis of the Arg304Gln factor VII defect (FVII Padua). *Acta Haematol, 124*, 229–234.