The higher prevalence of missense mutations in hemophilia B compared to hemophilia A could be important in determining a milder clinical phenotype in patients with severe hemophilia B

We thank Shetty *et al.*,[1] for their comments about the relationship between the type of mutation and clinical phenotype in hemophilia. As clearly mentioned in our manuscript,[2] the higher prevalence of missense mutations in hemophilia B compared to hemophilia A could be one of the most important factors possibly contributing to a milder clinical phenotype in patients with severe hemophilia B. Because the percentage of patients with missense mutations in hemophilia B may be as high as 60-70%,[3] as in our population (62% compared to 32% in hemophilia A), and because of the significantly lower incidence of hemophilia B than hemophilia A, comparing patients with null mutations between the two disorders would be very difficult, unless very large multicenter studies are undertaken.

As correctly pointed out by Shetty *et al.*, missense mutations, however, may cause a similar degree of factor deficiency as with null mutations, and the current classification simply states that severe deficiency is characterized by factor levels < 1 U/dL. It is not easy to measure levels below < 1 U/dL, thus one should rely on this threshold value to categorize patients with severe hemophilia, whatever the responsible mutation is. Perhaps in the future we will be able to revise this classification following a wider availability of very sensitive tests able to measure levels of < 1 U/dL. However, we should also keep in mind that even "null" mutations could allow for some protein to be produced because of alternative splicing in some splice mutations, or due to the presence of the readthrough mechanism, as demonstrated with nonsense mutations in hemophilia B.[4] Thus, further larger studies are needed to conclusively define the differences of clinical phenotype and the outcome of hemophilia A and B.

Daniela Melchiorre,[1] Silvia Linari,[2] and Giancarlo Castaman[2]

[1]Department of Experimental and Clinical Medicine, Section of Internal Medicine, University of Florence, Rheumatology Unit, Careggi University Hospital; and [2]Center for Bleeding Disorders, Careggi University Hospital, Florence, Italy

Correspondence: daniela.melchiorre@unifi.it

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