Factor VII deficiency: a cause of (or risk factor for) bleeding?

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Summary

Among the rare bleeding disorders factor VII deficiency is the most common, but correlating deficiency with bleeding phenotype is challenging. In their study Lou and colleagues investigate a large cohort of unrelated factor VII deficient patients providing a further perspective on the link between genotype and phenotype in this disorder.

Commentary on: Lou C, et al. Structural and functional characterization of novel *F7* mutations identified in Chinese factor VII deficient patients. Br J Haematol. 2023 (Online ahead of print). doi: 10.1111/bjh.18768

It is estimated that approximately 1 in 500,000 individuals worldwide have factor VII (FVII) deficiency.[1] Identification of genetic variants in patients with inherited disorders can provide useful insights regarding disease mechanisms, especially when genetic information is combined with relevant clinical information and data from functional / modelling assays to help determine whether / how a variant contributes to pathogenicity.[2,3] To date, the FVII variant database contains genotype / phenotype information linked to approximately 270 unique variants derived primarily from single case reports or small-scale studies of a few patients.[3] However, despite this abundance of information understanding the pathogenic mechanisms associated with FVII deficiency is difficult due to variability in the bleeding symptoms observed in patients with reduced FVII activity (FVII:C).[4] Patients with only a mild reduction in FVII:C can suffer from bleeding complications while patients with virtually undetectable FVII:C can be asymptomatic.[4,5]

Lou et al.[6] investigate a cohort of 50 unrelated Chinese patients presenting with FVII deficiency from a single clinical centre. Similar to previous studies,[3] a range of genetic variants is identified in these patients but the association with bleeding severity / symptoms is highly variable, including among gender- / age-matched patients with the same mutation and inheritance pattern.[6] The study also identifies novel genetic variants, with *in vitro* and *in silico* analyses confirming the association of these variants with a reduction in FVII:C and highlighting their influence on FVII interactions.[6] Despite this, for the majority of these novel variants the observed functional consequence does not translate to a significant bleeding phenotype.

Interestingly, in addition to recording bleeding severity / symptoms in their patients Lou and colleagues also report a bleeding score (BS) providing additional insight into the scale of bleeding in these patients.[6,7] Although BS has been reported in previous studies of FVII deficiency,[8,9] this is the first study to report BS in a large cohort combined with genotypic information. Notably, BS does not correlate with FVII:C in this cohort and in those patients exhibiting minor spontaneous bleeding the majority (63%) did not have a BS associated with excessive bleeding (Figure 1). A recent large study of Italian FVII deficient patients highlighted that compound heterozygous / homozygous mutations and mutations likely to truncate the FVII protein (frameshift,

nonsense, splice) were associated with lower FVII:C,[10] but neither aspect influences BS in the present study (Figure 1).

Although care should be taken not to over-interpret data from a single study, it does further highlight the complexity of bleeding in FVII deficient patients, emphasising that *F7* genotype may correlate with functional phenotype but not clinical phenotype. To conclude, further investigation of FVII patients combining extensive phenotypic information and whole genome sequencing data to account for the contribution of genetic / non-genetic factors would be beneficial to precisely elucidate the exact cause of bleeding diathesis in these individuals.

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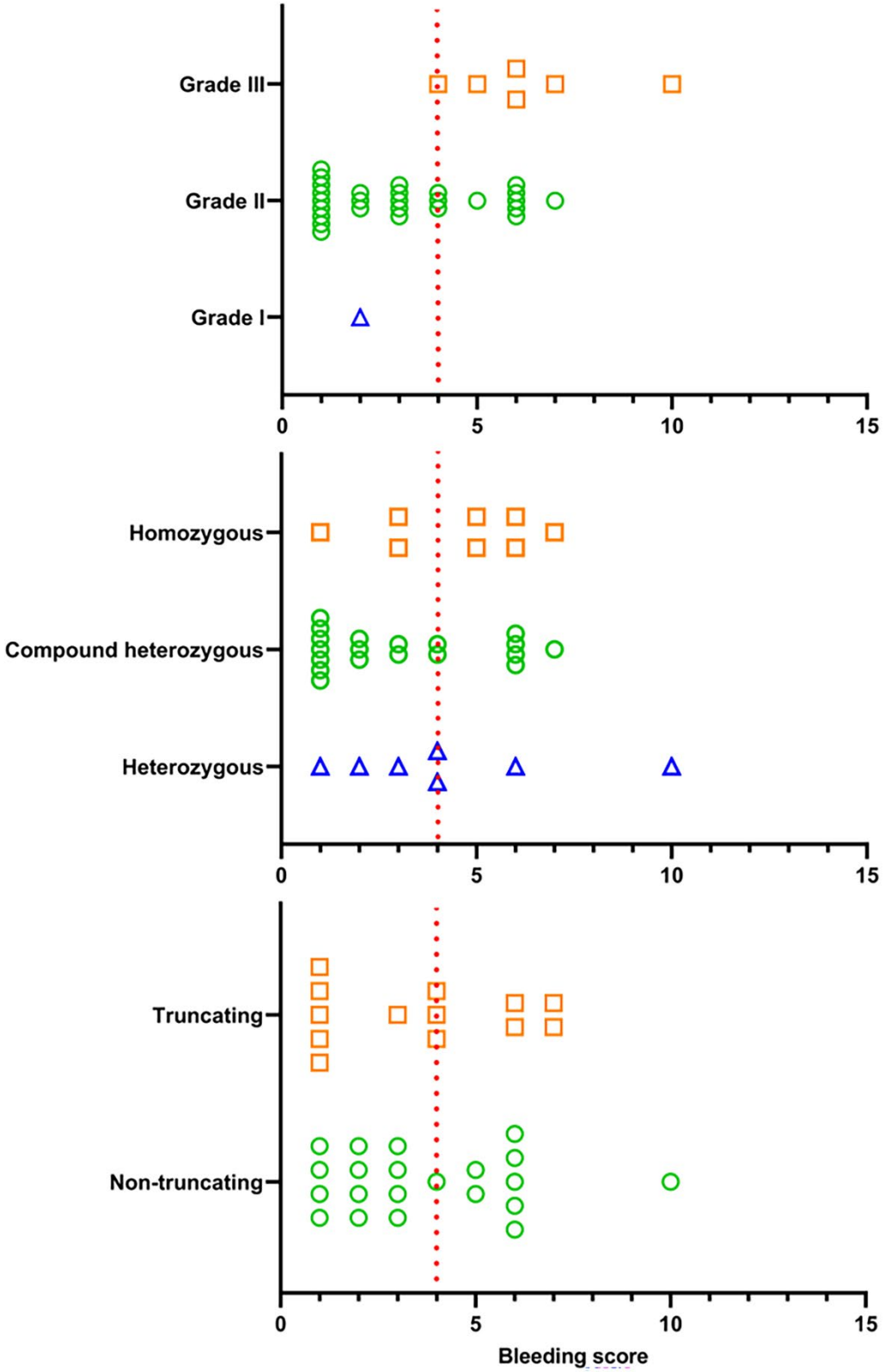

Figure 1. Bleeding scores reported in Chinese factor VII deficient patients in relation to bleeding severity,[4] inheritance of *F7* mutation(s) and type of mutation (criteria adapted from Quintavalle et al.[10]). A score of ≥4 indicates excessive bleeding.[7]