Factor VII Deficiency (FVII*Richmond, R304Q Mutant) Associated With Thrombosis

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Plasma of a 50-year-old woman who suffered from pulmonary embolism and deep vein thrombosis contained 1.2 U/ml of FVII antigen and ~0.14 U/ml FVII activity as measured using human tissue factor (TF). Sequence of all coding regions of the propositus' gene revealed a single point mutation (10828 G→A) that changes Arg-304 to glutamine in the protease domain of FVII. Single nucleotide primer extension technique established that both alleles carry the same mutation. A similar recombinant R304Q variant was expressed in a mammalian cell culture system using a Ca2+-dependent monoclonal antibody. The mutant, like normal FVII (VIIa), was rapidly activated to FVIIa by FXa. R304Q/VIIa/TF activated FX at ~16% of the rate obtained with VIIa. When limited TF and equimolar ratios of R304Q/VIIa and VIIa were used, the rate of FX activation was 67 ± 5% of that obtained with VIIa alone; the anticipated rate is 58% when the mutant competes equally with VIIa for TF sites. This indicates that R304Q/VIIa binds to TF with an affinity similar to that of VIIa. Modeling studies indicate that Arg-304 residue is internal in VIIa. Abolishing the positive charge of Arg-304 could disrupt the conformation of VIIa such that the substrate and/or the inhibitor binding for the enzyme are altered. This could impair regulation of clotting and may result in thrombosis.