

Homozygous Q100R Mutations in the Second EGF-Like Domain of Factor VII

To the Editor:

In their article (*Blood* 93:1237, 1999) Hunault et al report a patient homozygous for a CAG to CGG mutation in exon 5 of the factor VII gene, resulting in a Q100R alteration at the amino acid level. They claim that this is the first report of a homozygous patient with this mutation. We would like to draw their attention to the fact that we have described 22 patients from 16 apparently unrelated Norwegian families, of which 17 patients were homozygous for exactly the same mutation. We first reported these patients carrying the Q100R mutation at the XIVth Congress of the International Society on Thrombosis and Haemostasis,

New York 1993 (*Thromb Haemost* 69:612, 1993, abstr. no. 244) and later in a full publication (*Thromb Haemost* 79:1136, 1998). It is interesting to note the effect of modifying genes. Among our 17 patients, factor VII antigen varied from 10% to 28% of normal controls. The patient described by Hunault was reported to have 12%.

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Response

We appreciate this correspondence from Kavlie and Prydz that the identical mutation resulting in factor VII-Gln¹⁰⁰Arg was identified in homozygous form in 17 Norwegian patients with factor VII deficiency. As our report was submitted to *Blood* before publication of their manuscript in *Thrombosis and Haemostasis* in June 1998, we missed citing their report. The earlier abstract from 1993 did not mention that the patients were homozygous. Their manuscript confirms the hemorrhagic tendency associated with homozygosity for the factor VII-Gln¹⁰⁰Arg mutation. The results of the transient expression experiments with the mutant and wild-type cDNAs differ somewhat from ours because they obtained mean levels of factor VII antigen and activity of 57% and 6% of wild type in conditioned media from Chinese hamster ovary cells, respectively, while we obtained levels of 12% and less than 1% in COS-1 cells, respectively. This may be attributable to the use of different cell types and/or assay methods.

The differences in factor VII antigen levels among the Norwegian patients with homozygosity for this mutation are of interest, but it is somewhat surprising to see a substantial difference (28% and 11%), even among 2 young children from one of the families. We agree that there must be modifying genes or environmental influences to explain this difference.

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Long-Term Follow-up of a Randomized Study Comparing Cyclophosphamide and Total Body Irradiation With Busulfan and Cyclophosphamide for Patients Receiving Allogeneic Marrow Transplants During Chronic Phase of Chronic Myeloid Leukemia

To the Editor:

In September 1994 we reported the results of a randomized trial comparing 2 regimens to condition patients with chronic myeloid leukemia (CML) in chronic phase (CP) for allogeneic marrow transplantation.¹ Patients were treated between October 1988 and November 1992 and received marrow from HLA-identical siblings. Sixty-nine patients were treated with 120 mg/kg of cyclophosphamide and 6 daily exposures each of 200 cGy of total body irradiation (TBI), and 73 patients received 16 mg/kg of oral busulfan over 4 days followed by 120 mg/kg of cyclophosphamide (BU-CY). The 2 regimens had similar survival and relapse probabilities. The BU-CY regimen was better tolerated than the CY-TBI regimen. The median duration of follow-up in this study is now more than 7 years, and we report these outcomes updated to July 1, 1998.

Patients treated with the CY-TBI regimen (N = 69). In the initial

report, 29 patients had developed chronic graft-versus-host disease (GVHD) and 6 of these had died of causes not associated with relapse. Since then, 2 more of these patients have died of causes not associated with relapse and 2 additional patients (both of whom survive) have developed clinical extensive chronic GVHD.

In the initial report, 15 patients had cytogenetic relapse and none of these had died. The relapse was transient in 5 instances and these patients still survive in continuing remission without treatment. Of the 10 patients with persistent relapse, 3 have died in relapse, 4 are in cytogenetic remission after treatment with interferon (IFN) (polymerase chain reaction [PCR] status is positive in 2, negative in 1, and unknown in 1), and 3 are in continuing cytogenetic relapse despite IFN therapy. Since publication of the initial report, 6 patients have developed cytogenetic relapse between 2 and 6 years after transplant; 2 of these patients have died in relapse and 4 are being treated but remain in relapse.