A Novel Factor V Null Mutation Detected in a Thrombophilic Patient With Pseudo-Homozygous APC Resistance and in an Asymptomatic Unrelated Subject

To The Editor:

Pseudo-homozygous APC resistance is defined by finding the heterozygous factor V (FV) R506Q substitution (Leiden mutation) in the presence of APC resistance ratios similar to those of FV Leiden homozygotes. Although partial FV deficiency, invariably present in this condition, could compensate for the thrombophilic defect, all of the few cases reported so far are thrombophilic patients. The nature of the mutations responsible for FV deficiency in pseudo-homozygous APC resistance is still elusive, and their identification would make possible a more accurate diagnosis than that based on coagulation assays.

Fig 1. Syngeneic (A) and allogeneic (B) bone marrow engraftment after pretreatment with BU with or without CY. Male C57BL/6J lco (B6-Gpi-1b/Gpi-1b) mice (IFS Credo, L’Arbresle, France), 12 to 16 weeks old and weighing 25 to 30 g, were used as recipients. Congenic C57BL/6J-Gpi-1a/Gpi-1a (B6-Gpi-1a) and BALB.B10 mice (Jackson Laboratory, Bar Harbour, ME) were used as the source of syngeneic and H-2 compatible allogeneic donor bone marrow, respectively. Busulfan was injected intraperitoneally (IP) as a suspension in corn oil as fractionated doses (4 × 25 mg/kg) on 4 consecutive days. CY was administered (IP in phosphate-buffered saline, 200 mg/kg) 24 hours after (the last dose of) BU. BMT (10^6 bone marrow cells) was performed 24 hours after the last drug treatment or 48 hours after BU when CY was not in the regimen. Shown are the means (±SD, 4 to 6 mice per group) as percentages of Gpi-1a type erythroid chimerism up to 5 months after BMT. Asterisks indicate significance in Mann-Whitney-U test (*P < .01; **P < .05).

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We report here the case of a 57-year-old man with pseudo-
homozygous APC resistance who has experienced four thrombotic
episodes in the lower limbs since the age of 30: three deep vein
thrombosis episodes, two spontaneous and one following knee surgery
and immobilization, as well as a spontaneous superficial thrombophlebitis.
His 24-year-old daughter, who has inherited the FV Leiden allele
(Fig 1), also developed a superficial thrombophlebitis at 17 years of age.

Direct DNA sequencing of FV exons and splicing junctions was used
to search the whole FV gene for mutations. In the large exon 13 a
heterozygous C to T transition at nucleotide 2308 was found (Fig 1) that
affected the codon for Arg 712 (CGA), producing a stop codon (TGA)
and premature termination of translation. The resulting truncated
protein would lack the complete light chain (domains A3, C1, and C2).
This nonsense mutation, inherited by propositus’ son (Fig 1), also
casted the virtual absence of the non-Leiden mRNA, as demonstrated
by the homozygosity for FV Leiden after sequencing the FV cDNA
obtained from platelet RNA. These findings explain both FV deficiency
and marked APC resistance, because impaired expression of the
non-Leiden gene results in the only presence of FV Leiden molecules in
plasma.

Several recurrent mutations have been found in CpG sites within the
coagulation FVIII gene, which is very similar in size and structure to the
FV gene. Because the FV 2308 C to T transition at nucleotide 2308 was found (Fig 1) that
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