Contribution of low density lipoprotein receptor-related protein genotypes to coagulation factor VIII levels in thrombotic women

The contribution of low density lipoprotein (LDL) receptor-related protein (LRP) to variance of factor VIII (FVIII) levels in plasma was investigated in thrombotic women through analysis of frequent LRP genotypes. The G allele of the LRP -25C/G polymorphism, predicting increased LRP expression, was associated with 15% and 18% mean reductions of FVIII activity and protein levels, respectively. The combination of -25C/G LRP polymorphism with FVIII D1241E and ABO polymorphisms produced a gradient of FVIII levels, thus supporting the notion that several factors, acting in FVIII biosynthesis, post-translational modification and removal from circulation, have additive effects on the variance of FVIII levels in plasma.

Key words: LRP genotypes, FVIII levels, venous thrombosis.

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The FVIII levels observed in the present study (mean 1.87 IU/mL±0.62) were higher than those reported for other thrombotic cohorts. This difference could not be explained by the presence of overt inflammation. Since all the thrombotic patients in our sample were women, gender, a factor influencing FVIII levels, could have contributed to the observed higher FVIII levels. Patients were characterized for the -25C/G polymorphism of the LRP gene, which creates a new GC box potentially recognized by the transcription factor SP1. We found that the CG and GG genotypes, predicting increased LRP expression, were present in the fifth of the patients and were associated with a mean reduction of 0.28 IU/mL (15%) of FVIII activity levels (Table 1). We also observed a parallel effect on protein levels (mean reduction 18%) (Table 1). Only one G-carrier was present in the group of patients with the highest levels of activity (>90th percentile), whereas seven G-carriers were detectable in the group with the lowest levels (<10th percentile). In accordance with the hypothesis of a direct effect of FVIII levels on APC resistance, the mean APC sensitivity ratio was higher in G-carriers than in CC homozygotes.

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The finding that LRP genotypes modulate FVIII levels is an independent indication, in a human model of venous thrombosis, that LRP physiologically interacts with FVIII and that LRP gene variations are biologically plausible genetic determinants of FVIII levels. To test the hypothesis of additive effects produced by multiple genetic modulators of FVIII levels, patients were also grouped according to other known genetic determinants of FVIII levels, the FVIII D1241E substitution and ABO blood groups. A gradient of FVIII levels driven by genotypes was observed (Figure 1), with mean activity levels varying from 1.95 to 1.40 IU/mL for LRP/ FVIII, and from 2.02 to 1.32 IU/mL for LRP/ABO combined genotypes. The LRP/ABO genotypes jointly produced the largest mean difference (53%).

Although considering subjects with combinations of all markers led to small genotype groups this approach was explored to gain additional information. We found large mean differences (69%) ranging from 2.05 IU/mL for genotypes predicting higher FVIII levels (LRP -25CC/non O/FVIII DD) to 1.21 IU/mL for those associated with lower levels (LRP -25CG+GG/O/FVIII DE + EE). These data support the notion that several factors, acting in FVIII biosynthesis, post-translational modification and removal of the clotting factor from the circulation, have additive effects on the variance of FVIII levels in plasma.
Taking into account the relatively small contribution of LRP and FVIII genetic components to FVIII levels, large clinical studies are needed to establish the potential increased or decreased thrombotic risk conferred by these genotypes.

FB, GM and FM conceived and designed the study. CL and MC had a major role in the selection of thrombotic women, and performed and analyzed the clinical coagulation laboratory data. BL and MP performed the genotyping in all subjects. All authors critically contributed to the interpretation of the results. GM and FB wrote the paper. FB supervised the whole work and was responsible for the final approval of the version to be published. The authors declare that they have no potential conflicts of interest.

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