## Frequency of factor VIII intron 1 inversion in a cohort of severe hemophilia A Italian patients

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In the January 2003 issue of this journal, Tizzano EF *et al.*[1] reported their data on the frequency of the intron 1 inversion of the factor VIII (FVIII) gene in a cohort of Spanish hemophilia A (HA) patients. It seems now well established that the mutation is recurrent in severely HA patients, even though with a low frequency. To date, this mutation has also been investigated in the British[2] and in the German populations.[3] In Italy, data have been reported on 20 patients.[4] To provide further data on the frequency of this mutation in our country, we studied 93 patients with severe HA (residual FVIII activity <1%) referred to our Center from various Italian regions. They had previously been screened for intron 22 inversion and 39/93 (42%) were found positive. We tested the remaining 54 HA patients by PCR amplification for intron 1 rearrangement. Three/54 were found positive and their different haplotypes demonstrated that they were unrelated. The frequency of this mutation is 3.2% in all severe HA patients and 5% if we only consider patients who are negative for intron 22 rearrangement. This value agrees with those reported for other cohorts of hemophiliacs.[1,2,4]

The existence of a strong correlation between large gene rearrangements, such as inversions, large deletions, or stop codons, and a higher risk of inhibitor development has been reported.[5,6] In these cases a complete lack of endogenous circulating FVIII may be the cause of inhibitor formation. As reported in the literature the incidence of inhibitors in patients who are positive for intron 22 inversion is about 34%.[5] Since intron 1 inversion relies on a similar mechanism, it is conceivable that the presence of patients with inhibitors may occur with a similar frequency. Among our 3 patients who were positive for this inversion, one developed inhibitors which rose up to 4 BU after exposure to 2000 IUs of rFVIII, and increased to 128 BU following treatment with FVIII replacement due to an upper lip frenulum injury. Therapy with rFVIIa led to good control of the bleeding. Inhibitors have not been found in the other 2 mutated patients. On the basis of our own, and current literature data,[2,7] antibodies anti to FVIII have developed in 2/15 (13%) intron 1 positive patients. Apparently, the frequency of inhibitors in patients with intron 1 inversion is much lower than what has been observed in the cases mutated for intron 22 inversion. This discrepancy could be due to the low number of patients that have so far proven positive for intron 1 inversion. Since estimating the risk of developing inhibitors has relevant implications for the clinical management strategy, these preliminary data need further support in a much larger series of patients.

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