Possible Misdiagnosis of Factor VIII Gene Inversion in a Case of Severe Hemophilia A

To the Editor:

Hemophilia A, the commonest form of hemophilia, affects 1 in 5,000 males in the general population. This X-linked disease is often associated with mutations spread along the factor VIII gene. In a number of cases, no point mutations have been detected, but a strikingly abnormal mRNA transcript has been shown using Northern blot analysis. It has subsequently been found that large DNA inversions encompassing part of the factor VIII gene are responsible for this abnormality. This type of mutation accounts for half of the severe hemophilia A cases, whereas more classical mutations account for the remaining cases. The inversions may be due to the presence (close to and inside the gene coding for factor VIII) of three copies of an identical gene (F8A), thus favoring abnormal recombination events.

The detection of these inversions provides a very efficient way to analyze numerous cases at the molecular level, without the need of single-strand conformational polymorphism, denaturing gradient gel electrophoresis, or DNA sequencing. This rearrangement is routinely detected by Southern blot using Bcl I-digested genomic DNA, followed by hybridization with the p482.6 fragment. Five different patterns associated with inverted factor VIII gene have been described so far, but only two of them have been frequently observed.

As far as we know, no abnormal pattern has been reported for a normal allele. We report here on a sporadic case of severe hemophilia A. The DNA of the patient and that of his relatives was analyzed (Fig 1). No inversion was detected for the hemophilic; however, an unexpected band was surprisingly observed for the mother and for the two healthy brothers. The mutation thus segregated with the normal pattern, whereas the healthy factor VIII gene segregated with the additional band. Therefore, such a normal allele exhibits a novel intragenic polymorphism and the occurrence of this additional band should not be interpreted as the molecular signature of an inversion of the factor VIII gene (in this case, discrimination of the mutated from the normal allele was possible using the Bcl I polymorphism in the prospect of a prenatal diagnosis).

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