A Dutch family with moderately severe hemophilia B (Factor IX_{Heerde}) has a missense mutation identical to that of factor $IX_{London\ 2}$

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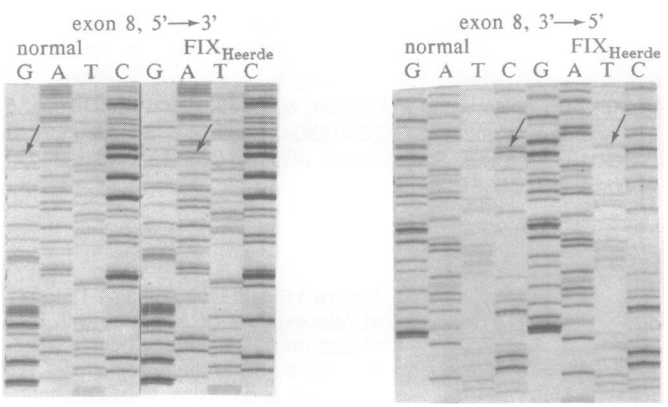
Genetic alterations in the factor IX gene that lead to impaired synthesis and/or aberrant molecules result in an X-linked recessive bleeding tendency (hemophilia B). Here we report a G → A transition at position 31119 (1), i.e. within exon 8 that codes for the larger part of the catalytic domain of factor IX, in a patient with moderately severe hemophilia B (FIX_{Heerde}) who has normal levels of factor IX antigen.

Exon 8 was amplified and sequenced as described before (2). In brief, 40 cycles of the polymerase chain reaction (3) were performed at 55°C with the exon 8 specific primers 5'-TCTGTGTATGTGAAATACTG-3'(nt 30769-30788 as in (1)) and 5'-GTTAGTGAGAGGCCCTGTTA-3'(nt 31431-31412). The amplified product of 663 bp was purified on agarose and directly sequenced using a commercial M13 sequencing kit (Boehringer Mannheim) and each of the amplification primers (80ng). The sequence analysis (figure) shows a G → A transition at position 31119 (1), which is identical to the mutation recently reported for factor $IX_{London2}$(4). The mutation predicts the substitution of ^{333}Arg by Gln. This apparently leads to an aberrant factor IX molecule with ~1% clotting activity and underlines the crucial role of ^{333}Arg for normal factor IX function. Furthermore, the occurence of the same mutation in two distinct geographic locations confirms that the CG dinucleotide involves a "hotspot" for mutation (5).



Part of the nucleotide sequence of the two orientations (5'→3' and 3'→5') of exon 8. The normal sequence is shown on the left and that from FIX_{Heerde} on the right. The nucleotide differences between the two sequences are indicated by arrows.

REFERENCES

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