National study of prevalence of the introns 1 and 22 inversions in F8 gene and its relation to inhibitors development to factor VIII in Mexican severe hemophilia A patients

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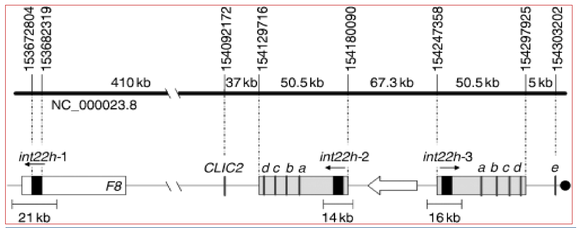
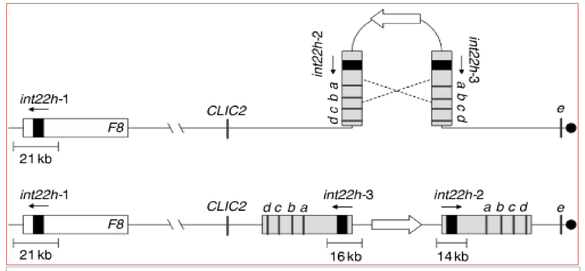
Introduction and objectives



The common palindrome configuration; above the X chromosome sequence (nucleotide number at relevant positions). [1]



Intra-chromosomal/chromatid homologous recombination yielding an inverted palindrome configuration. [1]

We investigated prevalence of Inv1, and Inv22-1/2, and its association as risk factors for inhibitors development to FVIII, in Mexican severe hemophilia A (HA) patients.

Results

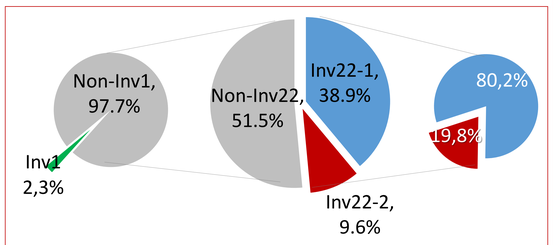


Figure 2. Inv22 and Inv1 prevalence in 167 unrelated Mexican families with severe HA. A prevalence of 48.5% for Inv22: 80.2% Inv22-1 and 19.8% Inv22-2, and 2.3% for Inv1 genotype.

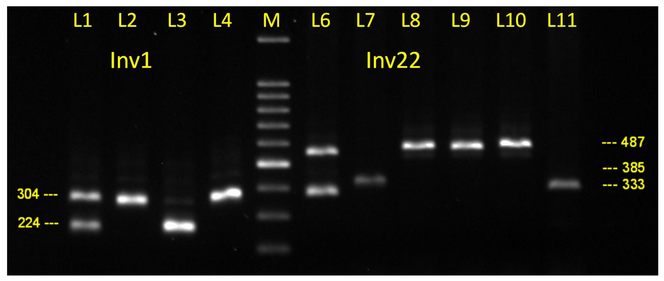


Figure 3. Inv22 and Inv1 products by IS-PCR on agarose gel electrophoresis. L1: Inv1 carrier; L2 and L4: non-Inv1 HA; L3: Inv1 HA. L6: Inv22-1 HA; L7: HA Inv22-2; L8–L10: non-Inv22 HA; L11: Inv22-1 HA. M: 100 bp.

Conclusions

Prevalence of Inv22 (48.5%) and Inv1 (1.2%) was similar to other populations. Inv1 was found for the first time in Mexican population in two independent families [3]. Inv22-1/2 or Inv1 positive patients showed lower risk for developing inhibitors with respect to patients without these severe mutations, but differences were not significant. Nevertheless, familial aggregation and inhibitor concordance in related patients indicate a significant genetic component to be explored in Mexican patients with severe HA.

Methods

We studied a cohort of 197 patients from 167 unrelated severe HA families, countrywide, for the detection of Inv1 and Inv22-1/2. All participants signed written consent.

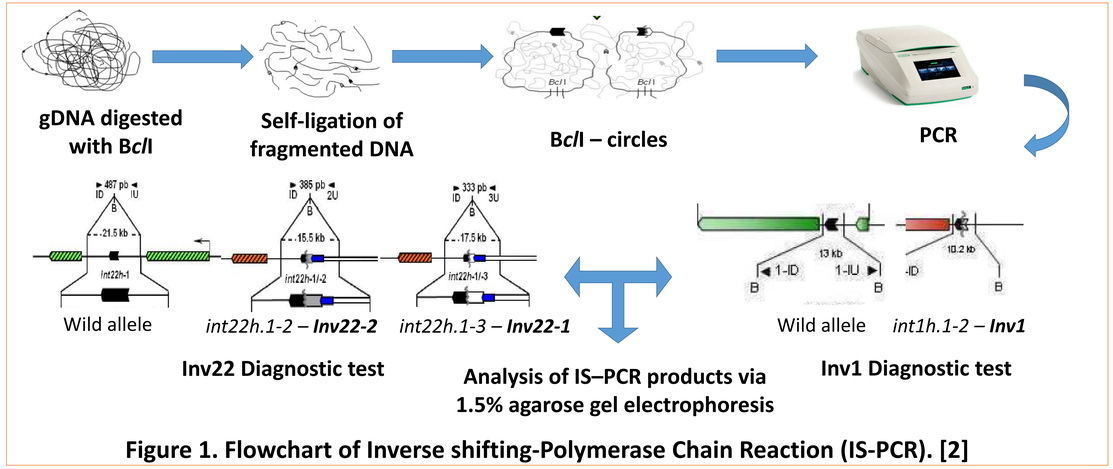


Figure 1. Flowchart of Inverse shifting-Polymerase Chain Reaction (IS-PCR). [2]

Median age of patients was 13 (1 – 58) years. 63.5% of cases were familial and the other 36.5% were sporadic. In two cases, Inv22-1 occurred *de novo* (non-carrier mother). Related patients shown familial concordance (78%) to develop or not develop inhibitors.

Genotype	Positive inhibitor	Negative inhibitor	Total
Inv22-1	26	52	78
Inv22-2	1	12	13
Inv1	2	3	5
Inv22-1/2, Inv1	**29 (30.2%)**	**67 (69.8%)**	**96**
Non-Inv22, Non-Inv1	34 (34.0%)	67 (66.0%)	101
Total of patients	**63 (32.0%)**	**134 (68.0%)**	**197**

Figure 4. Inhibitors to FVIII:C according to genotype in Mexican patients with severe HA. Only 29/96 (30.2%) patients with Inv22 or Inv1 genotype developed inhibitors (P = 0.357, Fisher exact test. RR: 0.897 CI 95%: 0.596–1.351).

References

1. Bagnall et al., *J Thromb Haemost* 2006;4:591–8.
2. Rossetti et al., *J Thromb Haemost* 2008;6:830–6.
3. Mantilla et al., *Am J Hematol* 2007;82:283–7