GENOTYPE-PHENOTYPE CORRELATION IN FAMILIES WITH MILD FACTOR VII DEFICIENCY

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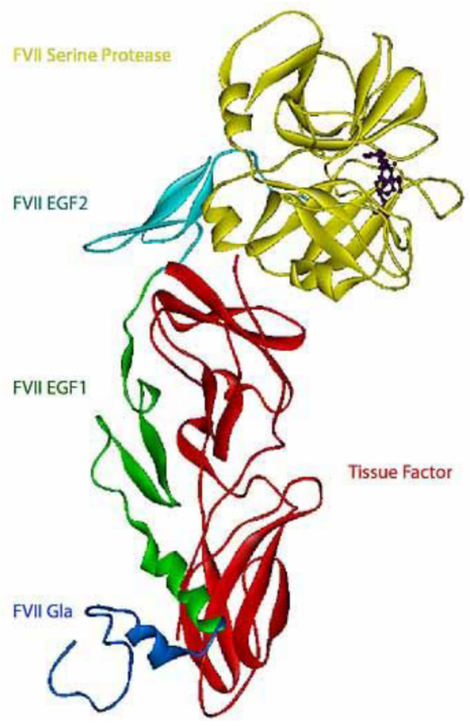
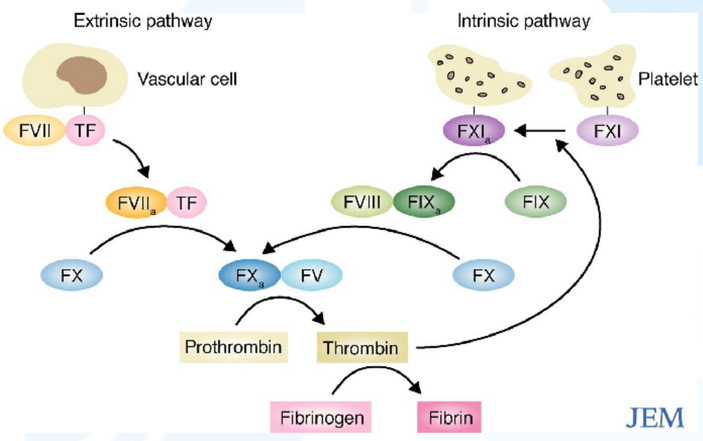
INTRODUCTION

FVII deficiency (MIM 227500) is the most common among the rare congenital coagulation disorders and is transmitted with autosomal recessive inheritance. Gene polymorphisms, pathological mutations, the presence of modifier genes and environmental factors could contribute to clinical heterogeneity, which ranges in severity from lethal to mild or even asymptomatic forms. The genotype-phenotype correlation is not always clear, and many cases seem to be difficult to establish the genetic influence on clinical phenotypes.



Factor VII protein



Extrinsic pathway

Family, member	FVII:C (IU/dl)[a]	Factor VII mutation	Polymorphic alleles[b]	Clinical symptoms
1, proband	21	c.985T>C p.Ser329Pro	A1A2, tc, M1M2	asymptomatic
1, mother	50		A2A2, cc, M2M2	asymptomatic
1, father	55	c.985T>C p.Ser329Pro	A1A1, tt, M1M1	Epistaxis, muscle hematomas
2, proband	38		A2A2, cc, M2M2	Gum bleeding
2, mother	>62		A1A2, tc, M1M2	asymptomatic
2, father	>62		A1A2, tc, M1M2	asymptomatic
3, proband	40		A1A1, tt, M1M1	asymptomatic
3, sister	>62		A1A2, tc, M1M2	asymptomatic
3, mother	>62	c.285G>A p.Glu95Glu (?)	A1A2, tc, M1M2	asymptomatic
3, father	>62		A1A2, tc, M1M2	asymptomatic
4, proband	39		A2A2, cc, M2M2	asymptomatic
4, mother	>62		A1A2, tc, M1M2	asymptomatic
4, father	>62		A1A2, tc, M1M2	asymptomatic
5, proband	40		A2A2, cc, M2M2	Gum bleeding
5, mother	>62		A1A2, tc, M1M2	asymptomatic
5, father	>62		A1A2, tc, M1M2	asymptomatic
6, proband	20	g.5120G>A c.64+5G>A	A1A2, tc, M1M2	prolonged bleeding
6, brother	22	g.5120G>A c.64+5G>A	A1A2, tc, M1M2	asymptomatic
6, mother	62		A1A2, tc, M1M2	asymptomatic
6, father	52	g.5120G>A c.64+5G>A	A1A1, tt, M1M1	asymptomatic
7, proband	33		A2A2, cc, M2M2	asymptomatic
7, mother	>62		A1A2, tc, M1M2	asymptomatic
7, father	>62		A1A2, tc, M1M2	asymptomatic

table 1: [a] normal range >62% as suggested by RBDD [b]A1/A2:promoter without/with CCTATATCCT insertion at -323; t/c nucleotide -122; M1/M2, R353Q

PATIENTS

In order to define clearly the genotype-phenotype correlation and to outline a welfare management of these patients, we evaluated seven families with mild congenital deficit of factor VII selected among all patients of Hub Haemophilia Centre of Parma (Italy). We focused our interest on these patients, collecting blood samples from all components of these families, not only from those with reduced FVII levels. The recruited families were formed by a proband, with reduced FVII:C (20%<FVII:C<40%, mean value: 33%), parents and siblings. Three probands did not show a bleeding tendency; the remaining patients showed gum bleeding or a mild but prolonged bleeding after injury. They all showed a prolonged prothrombin time (PT) carried out in occasional blood tests or pre-operative screening.

METHODS

The factor VII gene, including exons, flanking and promoter regions, were analysed by DHPLC and direct sequencing.

RESULTS

The activity levels, the genotyping results and the clinical symptoms for every family are presented in table 1. We characterized a pathological mutation in heterozygosis in two families (one missense and one splicing); in one family we detected a silent nucleotidic change of uncertain phenotypic effect. In the remainder, plasma levels of FVII are affected by polymorphisms known to be associated with low FVII:C but none of those patients had clinical manifestations. There remains undiagnosed mild deficiency of FVII in many patients due to a lack of significant bleeding symptoms.

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