SERVIZIO SANITARIO REGIONALE
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PHENOTYPE/GENOTYPE RELATIONSHIPS IN A LARGE COHORT OF PATIENTS WITH FACTOR VII DEFICIENCY

Regional Reference Centre for Inherited Bleeding Disorders

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Introduction and Objective Congenital Factor VII (FVII) deficiency is a rare bleeding disorder caused by mutations in FVII gene (F7) with autosomal recessive inheritance. A clinical heterogeneity and poor correlation with FVII:C levels are described. This study aimed to identify genetic defects and to evaluate their relationships with phenotype in a large cohort of patients with FVII:C <50%, from eight Italian Hemophilia Centres (HC).

FVII:C (Median; Range)	FVII:C ≤10% (0.8%; 0.4-7%)	10% <FVII:C ≤25% (22%; 13-25%)	25%<FVII:C ≤50% (36%; 27-49%)	TOTAL
Probands	**11**	**42**	**70**	**123**
Age (Median)	**44**	**27,5**	**25**	
M (%)	**6 (55%)**	**29 (69%)**	**44 (63%)**	**79 (64%)**
F (%)	**5 (45%)**	**13 (31%)**	**26 (37%)**	**44 (36%)**
Epistaxis	**2 (18%)**	**7 (16%)**	**5 (7%)**	**14 (11%)**
Bruising	**0**	**3 (7%)**	**2 (3%)**	**5 (4%)**
Menorrhagia	**2 (50%*)**	**2 (20%*)**	**8 (34%*)**	**12 (32%*)**
Spontaneous Muscle Hematoma	**4 (36%)**	**2 (5%)**	**0 (0%)**	**6 (5%)**
Gum bleeding	**0**	**0**	**0**	**0**
GI bleeding	**0**	**0**	**1 (1%)**	**1 (0.8%)**
CNS bleeding	**1 (9%)**	**0**	**0**	**1 (0.8%)**
Hematuria	**0**	**1 (2%)**	**0**	**1 (0.8%)**
Hemartrosis	**3 (27%)**	**0**	**0**	**3 (2%)**
Post Partum	**0**	**0**	**0**	**0**
Patients with bleeding	**7 (64%)**	**14 (34%)**	**19 (27%)**	**40 (33%)**
N Bleedings	**12**	**15**	**16**	**43**

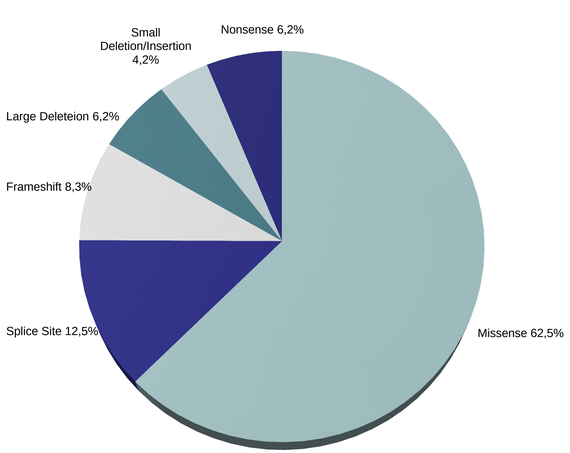

Figure 1: Type and rates of the mutations

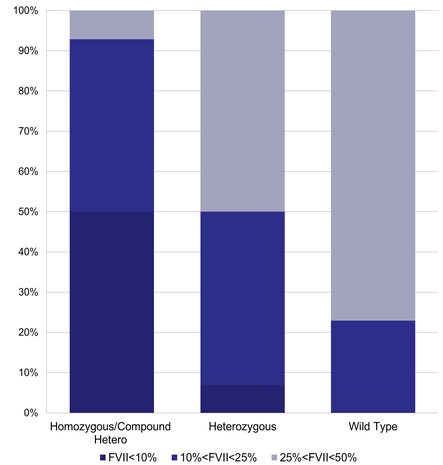

Figure 2: Genotype and FVII levels

Materials and Methods: The study was conducted in 154 patients (123 probands) with FVII:C <50% (11 with FVII:C≤10%, 42 with 10%<FVII:C ≤25%, and 70 with 25%<FVII:C<50%), selected because of a bleeding tendency or prolonged prothrombin time in routine or preoperative screening. We recorded clinical data and performed a molecular analysis by direct sequencing of the F7 gene (exons regions, exon/ intron boundaries and 5'untranslated region including the promoter). Patients were classified, depending on clinical manifestations into grades I (bleeding after trauma or antiplatelet/anticoagulant therapy), II (spontaneous minor bleeding) or III (spontaneous major bleeding) or into mild, moderate or severe categories according to the classifications by Peyvandi (JTH 2012).

Table 1: Baseline characteristics, rate and type of bleedings

Table 2: FVII:C levels vs Clinical bleeding severity (Peyvandi et al.)

Probands	Asymptomatic (n, %)	Grade I (n, %)	Grade II (n, %)	Grade III (n, %)
FVII:C <10%	**4 (36.4%)**	**No probands**	**3 (27.2%)**	**4 (36.4%)**
10%<FVII:C<25%	**28 (66.7%)**	**4 (9.5%)**	**9 (21.4%)**	**1 (2.4%)**
25%<FVII:C<50%	**51 (73%)**	**5 (7%)**	**14 (20%)**	**No probands**
Total	**83 (67%)**	**9 (7%)**	**26 (21%)**	**5 (4%)**

Results: Baseline characteristics of probands, rate and type of bleedings among the three groups of FVII:C levels are shown in Table 1, while Table 2 reports the severity of bleeding according to FVII:C.

Eleven probands had FVII:C ≤10%, 7 (64%) presenting symptoms were treated on demand (2-pdFVII, 5-rFVIIa) and one on prophylaxis. Five on 46 patients (11%) with 10%<FVII:C≤25% were treated on demand with rFVIIa. Eleven asymptomatic patients received rFVIIa for surgical prophylaxis. Among 97 patients with 25%<FVII:C≤50%, 27 (28%), 12 of them symptomatic, received treatment: 13 (14%) with pd/rFVIIa concentrate for major surgery, 14 (14%) with antifibrinolytics for minor procedures.

Figure 1 shows the type and rates of mutations. The distribution of genotype among the three groups is presented in Figure 2. Polymorphisms in promoter (NG_009262.1 (F7_v001):c.-326_-325insCCTATATCCT and NG_009262.1(F7_v001)c.-122T>C) and exon 9 were found in 3 patients with FVII<10%, 39 patients with 10%<FVII:C≤25% and 61 patients with 25%<FVII:C≤50% (Tab. 3).

Probands	no M + wt P	Het M + wt P	C. Het/homo M + wt P	No M+ Het P	Het M + Het P	C. Het/homo M + Het P	no M+ homo P	Het M + homo P
FVII:C <10	**-**	**4 (36%)**	**4 (36%)**	**-**	**-**	**2 (18%)**	**-**	**1 (9%)**
10%<FVII:C < 25%	**-**	**-**	**3 (7%)**	**8 (19%)**	**20 (48%)**	**3 (7%)**	**3 (7%)**	**5 (12%)**
25%<FVII:C <50%	**2 (3%)**	**6 (9%)**	**1 (1.5%)**	**4 (6%)**	**20 (28 %)**	**-**	**34 (48%)**	**3 (4.5%)**
Total	**2 (2%)**	**10 (8%)**	**8 (6,5%)**	**12 (10%)**	**40 (33%)**	**5 (4%)**	**37 (30%)**	**9 (7%)**

M= pathological variant, P= polymorphisms in the promoter region and in exon 9 wt= Wild Type; Het= heterozygosis; homo= homozygosis; C Het= compound heterozygosis

Table 3: Pathological mutations and polymorphisms according to FVII:C . Data are shown as N (%)

Conclusions: According to literature, we found a wide spectrum of F7 mutations and poor correlation with phenotype and FVII:C levels, indicating that modifier could modulate expressivity of FVII deficiency. Although some Authors considered that FVII:C>25% was necessary to remain asymptomatic, 27% of our patients with 25%<FVII:C≤50% presented spontaneous/provoked bleedings. Furthermore, the role of polymorphisms on phenotype and the correct management of mild deficiency remain open issues.

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