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Full Length Article

Rare bleeding disorders: Real-world data from a Spanish tertiary hospital

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ABSTRACT

Introduction: Due to their low prevalence, rare bleeding disorders (RBDs) remain poorly characterized.
Aim: To gain insight of RBDs through our clinical practice.
Methods: Retrospective study of the medical records of RBD patients followed up at the Central University Hospital of Asturias between January 2019 and December 2022.
Results: A total of 149 patients were included. Factor (F) VII (44 %) and FXI (40 %) deficiencies were the most common diagnosed coagulopathies. Most of the patients were asymptomatic (60.4 %) and the most frequent type of bleeding were mucocutaneous and after surgery. All replacement treatments were administered on demand and no patient was on a prophylaxis regimen. Currently available products were safe; allergic reactions after administration of plasma were the most frequent complication. Genetic analysis, carried out on 55 patients (37 %), showed that the most frequent mutations in RBDs are of missense type (71.9 %). We identified 11 different novel genetic alterations in affected genes. The c.802C > T (p.Arg268Cys) variant, previously described, was identified in 71 % (15 of 21) of the patients with FXI deficiency genotyped and none were related (probable founder effect).
Conclusion: Our study on an unusual large single center cohort of RBD patients portrays location-dependent distinct genetic drives and clinical practice particularities.

1. Introduction

Rare bleeding disorders (RBDs) account for 3–5 % of congenital coagulopathies and include deficiencies of the coagulation factors fibrinogen [factor (F)I], FII, FV, combined FV and FVIII, FVII, FX, FXI, FXIII, and congenital deficiency of vitamin K-dependent factors (VKCFDs). Most RBDs are transmitted as autosomal recessive traits; however, dysfibrinogenemia and some cases of FXI deficiency may be autosomal dominant. RBDs are reported in most populations, with a prevalence for homozygous or double heterozygous varying from 1 in 500,000 for FVII deficiency to 1 in 2–3 million for FII and FXIII deficiencies. Relative frequency varies among populations, being higher where consanguineous or endogamous marriages are common [1–3].

Due to the low prevalence of RBDs and the heterogeneity of the different registries, current knowledge on their genetics, diagnosis, clinical characteristics, and management remains limited. The World Federation of Hemophilia (WFH) (https://wfh.org) and the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) registry (https://www.ukhcdo.org/wp-content/uploads/2022/12/UKHCDO-Annual-Report-2022-2021-22-Data.pdf) collect data from thousands of patients with RBDs internationally and nationally, respectively. Other registries have been published over the years: the North American Rare Bleeding Disorders Registry (NARBDR) [4], the European Network of Rare Bleeding Disorders (EN-RBD) registry [5], and the Rare Bleeding Disorders in the Netherlands (RBiN) study [6,7]. Studies from a single center with a large cohort of patients have also been published: the Indian registry [8] and the VHrare study, in Spain [9]. Other studies have been limited to small groups of patients or to the analysis of a single RBD [10–16].

According to data extracted from the WFH and the EN-RBD, FVII and

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FXI deficiencies are the most frequently represented (37.5 % and 26.5 %, respectively) of the total affected population, followed by deficiencies of fibrinogen (8 %), FV (9 %), and FX (8 %), FXIII (6.5 %), and combined FV and FVIII (3 %), being FII deficiency the rarest disorder of them all (1.5 %) [3].

Here we present data on patients with RBD from our practice at the Central University Hospital of Asturias (HUCA), a center in northern Spain with a target population of one million inhabitants. Of interest, Asturias has an aging population, and certain regions within Asturias were geographically isolated until very recently. The rate of consanguineous marriages is low. The objectives of this retrospective real-world study are to provide with valuable additional data on RBDs through our clinical practice, by comprehensively reporting on epidemiological data, the type and severity of bleeding manifestations, the molecular analyses performed, and the treatment strategies and their complications. We also explored the relationship between genotype and laboratory phenotype (factor activity levels), and between laboratory phenotype and clinical bleeding severity. Our patient cohort was not included in the EN-RBD study [5], so we are certain that reporting it may contribute to widen the knowledge and improve the management of RBD patients.

2. Materials and methods

2.1. Data collection

Data were collected retrospectively from patients diagnosed with a RBD who were followed up between January 2019 and December 2022 at the Central University Hospital of Asturias (HUCA, Spain). The study is of descriptive nature, and all information was anonymized; informed consent or approval by the ethics committee was not required. As standard clinical practice, written informed consent was specifically requested for the genetic analyses performed.

Ten parameters were extracted from electronic patient files using a standardized data collection form (Table S1): (1) gender, (2) baseline factor level, (3) study age, (4) age at diagnosis, (5) circumstances leading to diagnosis [family history of disease, personal history of bleeding, or incidental finding after abnormal values of screening laboratory tests], (6) type of clinical manifestations, (7) bleeding severity, (8) treatment strategies, (9) treatment complications, and (10) genotype information, if available. Data was updated in December 2022.

2.2. Laboratory diagnosis

The clotting factor activity levels were measured according to the manufacturer's instructions (see Supplementary material for details). The cut-off values for the diagnosis of clotting factor deficiencies were < 50 %, except for fibrinogen which was < 150 mg/dL. Patients with factor levels between 50 % and 70 % were not included in order to increase specificity, thus avoiding false positive results and overdiagnosis. We have chosen this threshold for fibrinogen because it is the lower limit of normality in our laboratory. All deficiencies were confirmed in at least two determinations on different days, except in 4 patients in whom it was only performed once. Acquired factorial deficits such as those caused by inhibitor or FX depletion by amyloid fibrils, for example, were not evaluated in this work.

FII, FV, FVII, FX, FXI, and FXIII deficiencies were classified as severe or mild based on factor activity levels (< or ≥ 20 %, respectively). Fibrinogen deficiency was classified as severe if levels were < 50 mg/dL or mild if levels were between 50 and 150 mg/dL. No distinction was made between hypo- and dysfibrinogenemia.

2.3. Genetic diagnosis

Samples for genetic diagnosis, if performed, were sent to an external laboratory (Reference Laboratory S.A., L'Hospitalet de Llobregat, Spain). See Supplementary material for further details.

2.4. Severity of bleeding manifestations

Bleeding symptoms were classified into four categories based on severity according to EN-RBD criteria [5]: asymptomatic (no documented bleeding episodes), grade I [bleeding that occurred after trauma or drug ingestion (antiplatelet or anticoagulant therapy)], grade II [spontaneous minor bleeding (bruising, ecchymosis, minor wounds, oral cavity bleeding, epistaxis, and menorrhagia)], and grade III [spontaneous major bleeding (intramuscular hematomas requiring hospitalization, hemarthrosis, central nervous system, gastrointestinal, and umbilical cord bleeding)]. Patients were assigned to a certain category if they had at least one coincident documented episode and no higher-level episodes. Bleeding that occurs after surgery or an invasive procedure (tooth extraction, for example) is not specified in this classification; however, we have included these assumptions in the category of grade I.

2.5. Statistical analysis

Data are presented as means, medians, and percentages.

3. Results and discussion

3.1. Demographics and epidemiology

A total of 149 RBD patients were included. The mean study age of our cohort was 48 years and the median was 50 years (range: 4–92 years, excluding 5 patients who died throughout the study period due to non-hemostatic causes). The mean and median ages at diagnosis were 39 and 43 years, respectively (excluding 6 patients with unknown diagnosis date; Table 1). Twenty-three patients (15 %) were children (< 18 years) and 126 (85 %) adults. This predominance in adults seems to be a consequence of the mild nature of these disorders, which go unnoticed at pediatric age and are diagnosed over time as a result of routine blood tests or various hemostatic compromises (preoperative, trauma, or invasive procedures). The prevalence was similar between men (51 %) and women (49 %).

FVII and FXI deficiencies were the most frequent, representing 44 % ($n = 65$) and 40 % ($n = 59$) of the total, respectively (Table 1), being the latter represented in higher frequency compared to worldwide (26.5 %) [3]. No patients with FXIII deficiency or combined deficiencies of FV + FVIII or vitamin K-dependent factors were observed. Three patients had another additional alteration of hemostasis: one patient with FVII deficiency and another with FXI deficiency, both mild, had associated (mild) von Willebrand disease; one patient with mild FVII deficiency was also diagnosed with a platelet function defect.

Of the total of 149 RBDs, 58 (39 %) were classified as severe deficiencies and 91 (61 %) as mild deficiencies. The distributions for each disorder are shown in Fig. 1.

Table 1
Number and patient characteristics for each RBD (Total = 149). F, factor. The N is indicated next to the median study age or the age at diagnosis, in parenthesis, when there were missing values.

Deficiency	Study age (median, years)	Age at diagnosis (median, years)	Patients n (%)
RBD cohort	50 ($n = 144$)	43 ($n = 143$)	149 (100)
FVII	33 ($n = 63$)	22.5 ($n = 62$)	65 (44)
FXI	59 ($n = 56$)	50 ($n = 57$)	59 (40)
Fibrinogen	46	42 ($n = 12$)	13 (9)
FV	61	58	7 (5)
FII	63	30	3 (2)
FX	–	–	1 (<1)
Other combined (FV + FVII)	–	–	1 (<1)

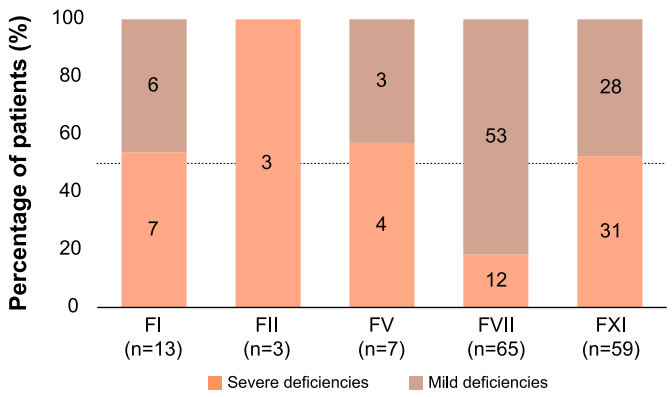

Fig. 1. Distribution of patients according to factor activity. FII, FV, FVII, FX, and FXI deficiencies were classified as severe or mild based on factor activity levels (< or ≥ 20 %, respectively). Fibrinogen (FI) deficiency was classified as severe if levels were < 50 mg/dL or mild if levels were between 50 and 150 mg/dL. Of the 13 patients with fibrinogen deficiency, seven (54 %) were labeled as severe and six (46 %) as mild. The three patients with FII deficiency had severe deficiency. Of the seven patients with FV deficiency, four (57 %) had severe deficiency and three (43 %) mild. Of the 65 patients with FVII deficiency, 12 (18 %) had severe deficiency and 53 (82 %) mild deficiency. The one case of FX deficiency (not represented) was severe. Of the 59 patients with FXI deficiency, 31 (53 %) had severe deficiency and 28 (47 %) mild deficiency. The only combined FV + FVII deficiency (not represented) was classified as mild.

3.2. Diagnostic circumstances

Of a total of 148 evaluable patients (unknown in one patient), the most frequent circumstance leading to the diagnosis was the incidental finding of abnormal coagulation values (111/148; 75 %) (usually as a result of preoperative screening and less frequently for other reasons), followed by positive family history (24/148; 16 %) and personal history of bleeding (13/148; 9 %). The events leading to diagnosis in RBD patients are illustrated in Fig. 2.

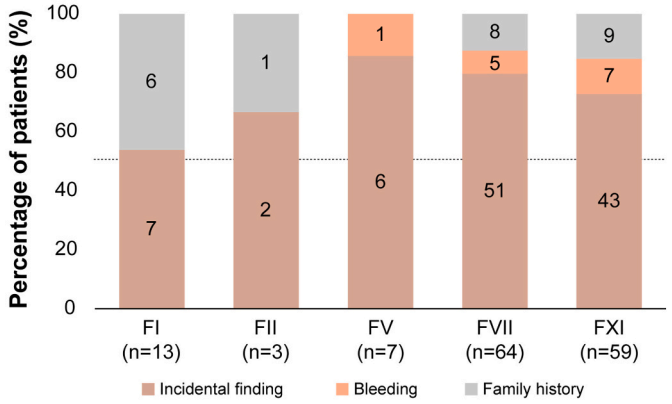

Fig. 2. Circumstances leading to diagnosis. Fibrinogen (FI) deficiencies were diagnosed as an incidental finding in seven (54 %) cases and by family history in six (46 %). Two (67 %) FII deficiencies were diagnosed as an incidental finding and one (33 %) due to family history. FV deficiencies were diagnosed as an incidental finding in six (86 %) cases and in one (14 %) case due to bleeding diathesis. Regarding FVII deficiency, 51 (80 %) cases were incidental findings, eight (12 %) cases were diagnosed by family history, and five (8 %) cases following bleeding. In one patient with FVII deficiency, it was not possible to identify the diagnostic event. The only FX deficiency (not represented) was an incidental finding. Of the patients with FXI deficiency, 43 (73 %) deficiencies were incidental findings, nine (15 %) were diagnosed due to family history, and seven (12 %) after a history of bleeding. The one combined FV + FVII deficiency (not represented) was an incidental finding.

3.3. Types and severity of hemorrhagic symptoms

In RBDs, the most frequent bleeding symptoms are mucocutaneous bleeding, as well as that after invasive procedures, as reported in our study. Unlike hemophilia, joint bleeding is rare and is mainly associated with FVII and FX deficiencies [2,3]. In general, bleeding in patients with RBDs is less severe than that in patients with hemophilia A or B with a similar degree of factor deficiency. In our cohort, 59 patients (39.6 %) presented some type of bleeding throughout their lives. The most frequent were cutaneous bleeding (16 %), heavy menstrual bleeding (HMB) [observed in 14 % (10/69) of women ≥ 14 years of age], excessive bleeding after surgery (10 %), epistaxis (8 %), and oral bleeding (8 %). Less common symptoms were gastrointestinal, cerebral, joint, and muscle bleeding (2 %, 2 %, 1 %, and 1 %, respectively). Fig. 3 describes all bleeding symptoms and the contribution per factor deficiency.

HMB was reported previously in 50 % of women with RBDs independently of the RBD type [2]. In our cohort, HMB was observed in a small percentage of women, as assessed based on their personal opinion. The subjective perception by the patients, accustomed to heavy bleeding since childhood, and which they see as normal, could be an important cause of underestimation and the reason behind the discrepancy with previous studies.

Regarding the bleeding severity, 90 patients (60.4 %) were asymptomatic. Grade I, II, and III bleeding were observed in 32 (21.5 %), 22 (14.8 %), and 5 (3.3 %) patients, respectively (Fig. 4). The patients with grade III bleeding were a severe FII deficiency patient with spontaneous hemarthrosis, a mild FV deficiency patient who presented a hypertensive cerebral bleeding (advanced age, no antithrombotic therapy), a severe FVII deficiency patient who presented two spontaneous hemarthrosis episodes in the left ankle, a mild FXI deficiency patient diagnosed with salmonellosis and gastrointestinal bleeding, and an elderly severe FXI deficiency patient with hypertension who presented a chronic subdural hematoma. The other patient who suffered a cerebral hemorrhage had a mild FXI deficiency but was of advanced age and under anticoagulant treatment with antivitamin K, therefore, it was considered a triggered event (grade I). Bleeding symptoms in our cohort were slightly milder than in the EN-RBD study (where 45.8 % of patients

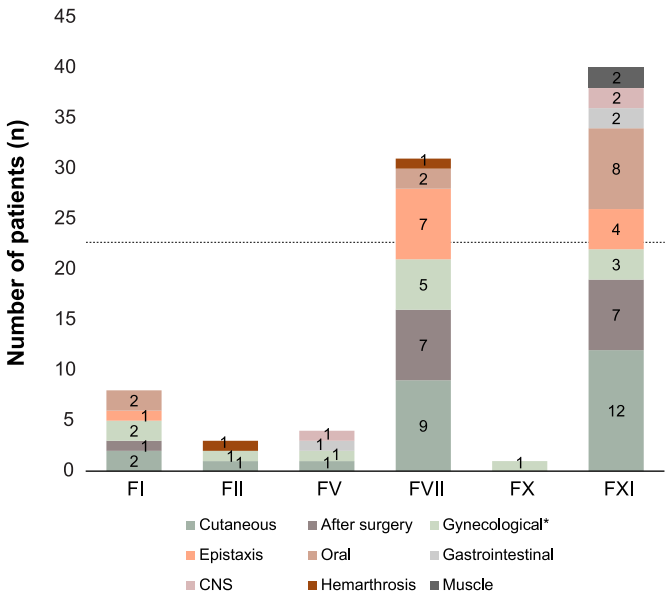

Fig. 3. Types of bleeding for each deficiency. n = number of patients who ever had this type of bleeding. The same patient can have several types of bleeding. CNS: central nervous system. * Includes 10 patients with heavy menstrual bleeding, two patients who presented postpartum hemorrhage, and another patient who presented miscarriage-related bleeding.

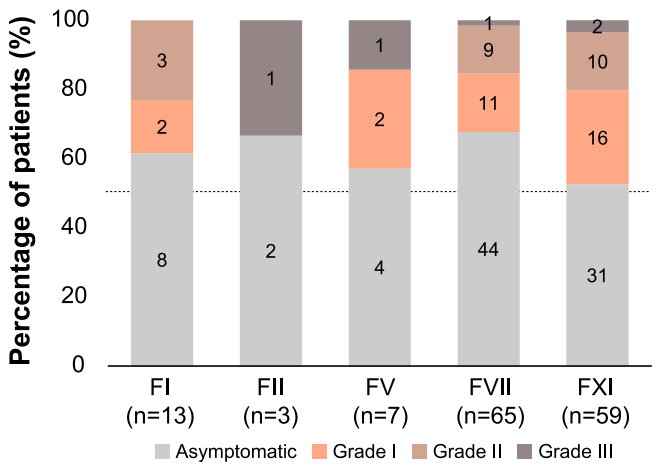

Fig. 4. Distribution of bleeding severity categories according to RBD. Not shown in the figure: the patient with FX deficiency had grade I hemorrhagic symptoms; the patient with combined FV + FVII deficiency was asymptomatic.

were asymptomatic) [5] and much milder than in the Dutch registry (where only 8 % of patients were classified as asymptomatic, with 60 % of patients with grade II hemorrhages) [6]. We think that this difference, more accentuated with respect to the Dutch cohort, is probably due to subjectivity when reporting bruises and their circumstances (both by the doctor and the patient), being grade II if they are considered spontaneous, in addition to the high occurrence of menorrhagia in the Dutch registry (77 % of all women aged 14 years or older).

Clinical symptoms in RBDs vary significantly between disorders and patients, even when affected with the same disorder [3]. Factor activity can help predict the frequency and severity of bleeding manifestations, especially in fibrinogen, FII, FX, and FXIII deficiencies. For FV and FVII deficiencies, there is weak association, while there is no clear correlation for FXI deficiency [5,17]. In our study we have evaluated this relationship for the most frequent deficiencies (Fibrinogen, FV, FVII, and FXI; Fig. S1). We have not found any correlation between factor levels and bleeding severity; however, in fibrinogen and FV deficiencies the correlation is difficult to assess, due to the small number of patients for each one.

3.4. Treatment strategies

Therapeutic management in these patients is difficult and based on the consensus of experts rather than on evidence-based guidelines, although there are recommendations at an international level [18–21]. As a general rule, treatment for most RBDs is on demand and should generally be maintained until the bleeding episode has resolved, 1–3 days after minor surgery, or until the surgical wound has healed in cases of major surgery. In especially severe cases, secondary prophylaxis will be considered based on the frequency of bleeding and the risk of severe spontaneous bleeding. Except for severe FXIII deficiency, there is no consensus on primary prophylaxis for RBDs. In our registry, 53 % (79/148) of the patients received replacement therapy at some point in their lives (we lacked treatment information from one FXI deficiency patient). All replacement treatments were administered on demand, in the context of either invasive procedures or for the treatment of bleeding episodes. No patient died after spontaneous or postoperative bleeding. No patient was on a prophylaxis regimen. In decreasing order of frequency, the products used were: Fresh frozen plasma (FFP), recombinant activated FVII concentrate (rFVIIa), fibrinogen concentrate, and non-activated prothrombin complex concentrate (PCC). Plasma-derived FXI concentrate, which has been associated with thrombotic events [22], is not available in our center. Non-replacement treatment was not evaluated. Table 2 details the treatments received and the number of patients within each diagnosed deficiency who received a certain treatment at least once.

Table 2
Products used for each deficiency. Only replacement therapy was considered.

Treatment	Number of patients who received the treatment at least once[a]					
	FI	FII	FV	FVII	FX	FXI
FFP[b]	0	1	5	5	1	33
PCC[c]	0	2	0	0	0	0
Fibrinogen concentrate	6	0	0	0	0	0
rFVIIa[d]	0	1	0	27	0	0
None	7	0	2	34	0	25

[a] The same patient could receive more than one type of treatment. In one patient with FXI deficiency we have no information about treatments received.
[b] Fresh frozen plasma.
[c] Non-activated prothrombin complex concentrate.
[d] Recombinant activated FVII concentrate.

3.5. Treatment-related complications

Currently, once the risk of infections inherent to human-derived bioproducts has been overcome, the most relevant treatment-related adverse events are inhibitor development, hypersensitivity reactions, and thrombotic complications. Cases of autoantibodies following replacement therapy have been reported in fibrinogen, FII, FVII, FXI, and FXIII deficiencies [3].

In our study, 4 patients (1 with FVII deficiency and 3 with FXI deficiency) experienced an allergic reaction to FFP. A patient with FVII deficiency presented a superficial venous thrombosis in the right lower limb after a surgically treated hip fracture while receiving treatment with rFVIIa at a dose of 15 μg/Kg/24 h (but the patient had a history of 2 previous venous thrombosis, and prophylactic heparin had been withdrawn due to anemia). A patient with severe FII deficiency and significant hemorrhagic symptoms that had received rFVIIa and PCC in the past in addition to "multiple transfusions" (unspecified) during the 70s and 80s was seropositive for human immunodeficiency virus (HIV) and hepatitis C virus (HCV). No other seroconversion was documented in any other patients. Inhibitor development was not suspected in any case. No patient with fibrinogen deficiency presented complications related to the administration of commercial fibrinogen concentrates.

3.6. Genotype

Demonstration of a molecular defect is useful for diagnosis of RBDs, but not required. Missense mutations are the most frequent cause of RBDs, accounting for 50–80 % of known gene variations, except combined FV + FVIII deficiency due to mutations on *LMAN1*, for which the most common gene variations (50 %) are insertions/deletions. Insertions/deletions represent 20–30 % of gene variations of the fibrinogen, *F5*, *MCFD2*, and *F13A* genes and < 15 % of the remaining coagulation factor genes. Splicing and nonsense mutations comprise 5–15 % of all identified mutations in all coagulation factors, with a maximum rate of 20 % in the *LMAN1* gene [23]. Despite significant advances in the field, approximately 5–10 % of affected patients with severe deficiencies have no identifiable genetic defects [3], which may be due to alterations in non-coding regions, large heterozygous deletions, or large genomic rearrangements. In these cases, alternative approaches include multiplex ligation-dependent probe amplification (MLPA) for the identification of large deletions/duplications and long PCR for the detection of exon deletions [24].

In our cohort, genetic analysis was performed in 55 patients (37 %) (Tables S1–S2); the vast majority of cases (53/55) were not related. Al least one mutation was identified in 51 patients (93 % of the cases studied). In the four cases where a variant was not identified, we did not extend the study by performing MLPA. Sixty-six expected disease-

associated alleles were identified, for a total of 32 different variants; the most frequent were missense type (see Fig. 5).

The 11 genotyped patients with fibrinogen deficiency (five severe and six mild) had a heterozygous mutation. The three patients with FV deficiency, which was severe, were double heterozygotes. In the patient with (mild) combined FV + FVII deficiency, a heterozygous mutation was identified in the *F5* gene and none in the *F7* gene. Of the 18 patients with FVII deficiency, the three who presented a severe deficiency were double heterozygotes; of the 15 patients with mild deficiency, 11 were heterozygotes and one was homozygote, and in three patients, no mutation was found. The most frequent molecular alteration in FVII deficiency [present in 33 % of the patients studied (6 of 18) and none were related] was the known polymorphism c.1238G > A p.Arg413Gln (missense type), formerly p.Arg353Gln. Polymorphisms in F7 gene can cause low levels of FVII:C being associated with a mild clinical phenotype. The alteration c.1238G > A in heterozygous and homozygous state is associated with reduced FVII:C levels of 20–25 % and of about 50 % in circulating plasma respectively [25–27]. The patient with severe FX deficiency was double heterozygous.

Of the screened 21 patients with FXI deficiency, most of the severe cases (15/16) were homozygous or compound heterozygous except one, who was heterozygous. Of the five patients with mild deficiency, two were heterozygous, one was double heterozygous, one had two homozygous and heterozygous variants, and there was one negative study. The most frequent mutation [identified in 71 % of the patients studied (15/21) and none were related] was the c.802C > T (p.Arg268Cys) missense variant in the F11 gene (exon 8) that affects the apple 3 domain of the protein, classified as probably pathogenic, and has been described previously in the literature in 6 cases: two related patients in another area of Spain (southeast) [28] and four patients in the United Kingdom [29, https://f11-db.eahad.org (accessed on August 22, 2023)]. This variant is annotated in the dbSNP database (rs763496524) and has a population (total) frequency of 0.0074 % and 0.0 % in the population of Ashkenazi Jews, according to gnomAD. Considering the very high proportion of unrelated individuals with FXI deficiency who have this mutation in our area (71 %), and the fact that the frequency of FXI in our region is increased compared to the frequency reported worldwide (26.5 %) [3], we could consider it a variant with a founder effect. The mutation is not described in The Mediterranean Founder Mutation Database (MFMD, http://mfmd.pasteur.ma).

Interestingly, we identified 11 different previously unreported genetic alterations: c.1474 T > G (*FGB*), c.1552delG (*FGA*), c.1202 A > G (*F5*), c.3181G > T (*F5*), c.1763-1G > T (*F5*), c.289 A > G (*F7*), c.1237C > T (*F7*), c.1248G > T (*F7*), c.1264G > C (F7), c.1327 T > G (*F7*), and c.98_100del (*F10*).

Overall, excluding fibrinogen deficiency, of the 23 patients with severe RBDs genotyped, 22 (96 %) showed a homozygous or compound heterozygous genotype and only 1 (4 %) was heterozygous. Of the 21 patients with mild RBDs genotyped, 14 (67 %) were heterozygous, 3 (14 %) were homozygous or compound heterozygous, and in 4 (19 %) no mutation was found. Therefore, as expected, a relationship between genotype and laboratory phenotype was observed, since the majority of patients with factor activity levels < 20 % were homozygous or compound heterozygotes and those with levels > 20 % were predominantly heterozygotes. However, in fibrinogen deficiency, the 11 patients studied were heterozygous, even those with undetectable Clauss fibrinogen values. Therefore, we could not establish a relationship between the intensity of the fibrinogen deficiency and the genotype, since dysfibrinogenemias follow a dominant pattern with frequently missense heterozygous mutations.

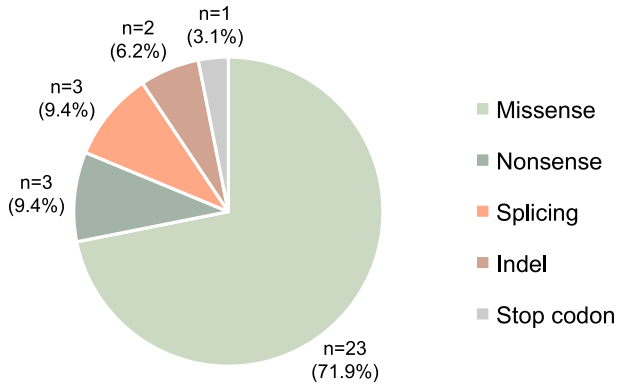

Fig. 5. Frequency distribution of mutation types. In total 32 different mutations were identified. n = number of different mutations.

3.7. Limitations

The first and main limitation of our study is the small number of patients per deficiency, which is inherent to the rarity of these disorders and the casuistry of a single hospital. Therefore, we could not assess differences between different RBDs, in terms of types and severity of bleeding, for example. Furthermore, our region has geographical and social characteristics that condition the demographics of the study. Secondly, the cut-off point used for the diagnosis of RBD was a factor activity of 50 %, so we are not evaluating patients with very slight deficits (levels of 50–70 %). Thirdly, we have not made a distinction between type 1 and type 2 deficiencies, since only a functional method was used to measure the activities of all factors, except in cases of suspected FXIII deficiency, for which an antigenic assay was used. In this sense, no FXIII deficiency was diagnosed. We do not believe that this was due to the use of an antigenic method, incapable of detecting qualitative defects, since there is solid evidence that antigenic tests show excellent correlation with functional ones [30]. Factor antigenic assays are essential for diagnosing fibrinogen and FII deficiencies, allowing appropriate classification and treatment of patients with dysfibrinogenemia and dysprothrombinemia. Fourthly, we have divided the deficiencies into mild or severe based on an activity level of 20 % (50 mg/dL for fibrinogen), following the thresholds for bleeding risk proposed by the French Reference Centre on Haemophilia and Rare Bleeding Disorders (FRCH) [21] and according to the criteria requested for certification of CSUR (Reference Centres, Departments and Units) of the National Health System in Spain. However, with the exception of FXI deficiency, other classifications have also categorized the laboratory phenotype for the different RBDs into mild, moderate, and severe according to activity levels associated with an asymptomatic clinical course, triggered or mild spontaneous bleeding, and severe spontaneous bleeding, respectively [17]. Finally, as this is a retrospective collection of data, there may be incomplete information and bleeding scores or pictorial blood loss assessment charts were not used, so we think that bleeding symptoms are probably underestimated.

4. Conclusion

Few studies have evaluated these rare coagulation disorders (Table 3), the vast majority being based on small patient cohorts. This study was initiated with the aim of garnering greater knowledge about these rare coagulopathies, and to add valuable information considering the particularities of our region. In spite of the acknowledged limitations, this article reports real-world data from a large cohort of RBD patients from a single institution. The incidence in our region seems higher than that reported in the literature. This observation reveals the tendency to underdiagnose RBDs, which go unnoticed in most cases due to their mild hemorrhagic phenotype. The results shown in this article are a summary of its main characteristics and reproduce what we currently know from the literature. Most patients are asymptomatic or have mild hemorrhagic symptoms, with an incidental finding being the most common circumstance that leads to diagnosis. The most common disorders are FVII and FXI deficiencies. Overall, the most frequent

Table 3
Selection of previously published RBD studies.

Study	NARBDR [4] (n = 294)	EN-RBD [5] (n = 489)	RBiN study [6][a] (n = 263)	India [8] (n = 281)	VHrare study [9] (n = 101)	Present study (n = 149)
Type	Multicenter (58 centers)	Multicenter (13 centers)	Multicenter (6 centers)	Single center	Single center	Single center
Geographic scope	USA and Canada	Europe (different countries)	National (Netherlands)	Vellore (Southern India)	Barcelona (Northeast Spain)	Oviedo (North of Spain)
Demographics	Median age at diagnosis: 7 years. No distinction was made by sex	Mean age at the time of data collection: 31 years. Women: 51 %	Median age at time of inclusion: 38.5 years Adult women: 49 % Adult men: 29 % Children: 22 %	Median age at diagnosis: range 9.5-19.3 years	Median age at diagnosis: 27.67 years. Men: 52.47 %	Median age at diagnosis: 43 years. Men: 51 %
Diagnostic criteria	Factor activity below the thresholds (unspecified)	Factor activity below the thresholds (unspecified)	Factor activity below the thresholds (unspecified)[b]	Factor activity <50 %	Included severe deficiencies only (defined by factor activity <20 %)	Factor activity <50 %
Most frequent RBDs	FVII (46 %) FXI not included	FVII (38 %) FXI (22 %)	FVII (22 %) FXI (16 %) Fibrinogen (16 %)	FXIII (31 %) FXI the rarest (4 %)	FVII (36 %) FXI (24 %)	FVII (44 %) FXI (40 %)

n = number of patients.
[a] Included fibrinolysis disorders.
[b] Or if there was a pathogenic heterozygous, compound heterozygous, or homozygous variant.

symptom is mucocutaneous bleeding and that after invasive procedures. The diagnosis of RBDs is independent of the genotype, but if it is analyzed, a genetic alteration is identified in most cases, with the most frequent mutations being missense. We have identified 11 novel mutations. Unexpectedly, we have identified one variant (c.802C > T) with a probable founder effect in patients with FXI deficiency. There is an association between genotype and laboratory phenotype: homozygote or compound heterozygote patients typically show severe deficiencies, whereas heterozygotes show mild deficiencies. No correlation was found between the laboratory phenotype and the clinical phenotype in terms of severity in the 2 most frequent and evaluable disorders in our study (FVII and FXI deficiencies). Currently available treatments are safe, and plasma allergy is the most common documented complication.

Multicenter registries are inherently associated with great variability in diagnosis and also the diagnostic criteria are different between the different studies. Participation in national and international registries is necessary to obtain more information about these disorders. Harmonization in data collection and standardizing diagnostic criteria should be objectives to be achieved.

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Disclosure

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CRediT authorship contribution statement

Daniel Martínez-Carballeira: Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alberto Caro:** Writing – review & editing, Data curation. **Ángel Bernardo:** Writing – review & editing, Data curation. **José Ramón Corte:** Writing – review & editing, Data curation. **José Carlos Iglesias:** Writing – review & editing, Data curation. **Isabel Asunción Hernández De Castro:** Writing – review & editing, Data curation. **Laura Gutiérrez:** Writing – review & editing, Visualization, Software, Investigation, Funding acquisition, Formal analysis. **Inmaculada Soto:** Writing – review & editing, Data curation.

Declaration of competing interest

The authors declare no conflicts of interest.

Data availability

The data that supports the findings of this study are available in the supplementary material of this article.

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