

# Expanded clinical, genetic, and biological spectrum of filaminopathies with hematological involvement

Constitutional thrombocytopenias represent a heterogeneous group of rare diseases where thrombocytopenia can signal complex, multi-organ disorder. One example is filaminopathy A, a very rare and probably underdiagnosed disease<sup>1</sup> that accounts for approximately 1% of inherited thrombocytopenias (unpublished data from the French reference center for inherited platelet disorders [CRPP], 2025). It is caused by variants in the *Filamin A (FLNA)* gene. This gene, located on the X-chromosome, encodes a ubiquitous actin-binding protein interacting with over 90 partners involved in intracellular signaling and cytoskeletal reorganization.<sup>2</sup> Among its many roles, FLNA is known to interact with proteins involved in platelet production and activation, such as  $\alpha$ IIb $\beta$ 3 (GPIIb/IIIa) and GPIb, supporting its role in thrombopoiesis and platelet functions.<sup>2</sup> Thrombocytopenia is a recognized but variably penetrant manifestation. A recent literature review regrouping 170 patients carrying pathogenic *FLNA* variants reported platelet abnormalities in 11 individuals, although hematological data were missing for most cases, suggesting potential under-reporting.<sup>3</sup> A classical feature occurs in females carrying a null *FLNA* variant responsible for a loss-of-function of the protein. These patients typically present with periventricular nodular heterotopia (PNH), seizures, Ehlers-Danlos-like connective tissue symptoms, and macrothrombocytopenia. Several teams have shown that females harboring a null variant have two platelet subpopulations, one lacking FLNA.<sup>4</sup> In hemizygous males, null *FLNA* variants can cause severe or fatal perinatal manifestations.<sup>5</sup> In contrast, the pathogenicity of missense variants remains debated. Some have been reported as potentially pathogenic, but apart from those affecting the first 150 amino acids (exon 2) and impairing FLNA-actin binding, little is known about how others affect platelet phenotype and the underlying mechanisms.<sup>5-7</sup> Thus, classifying missense *FLNA* variants in thrombocytopenic patients with suspected milder filaminopathies is challenging.

This study retrospectively collected clinical and biological data from patients referred to the CRPP with *FLNA* variants. It aimed to describe a large cohort of patients with *FLNA* variants and hematological involvement and identify indicators suggesting filaminopathy as the underlying cause of thrombocytopenia. Flow cytometry measurement (FCM) and immunofluorescence (IF) were used to assess intraplatelet FLNA in patients and controls. Sixteen *FLNA* variants were studied in 18 patients, including two relatives (Figure 1A). All cases were included after informed consent in accordance with the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (NCT04419987). Variants were identified using a gene panel sequencing for platelet disorders,

as previously described.<sup>8</sup> This is the largest cohort to date focusing on hematological manifestations of filaminopathy A. Patients were categorized according to the type of *FLNA* variants. The first group, with a null variant, had a classical phenotype, including PNH as a discriminating feature, along with cardiac and vascular defects, hyperlaxity, and gastrointestinal and pulmonary disorders. All had FLNA-negative platelets. The second group had missense variants, absent or rare in general population databases, with computational evidence of deleterious effects on the protein. They had a subtler phenotype, lacked FLNA-negative platelets, and sometimes had an alternative diagnosis explaining their thrombocytopenia.

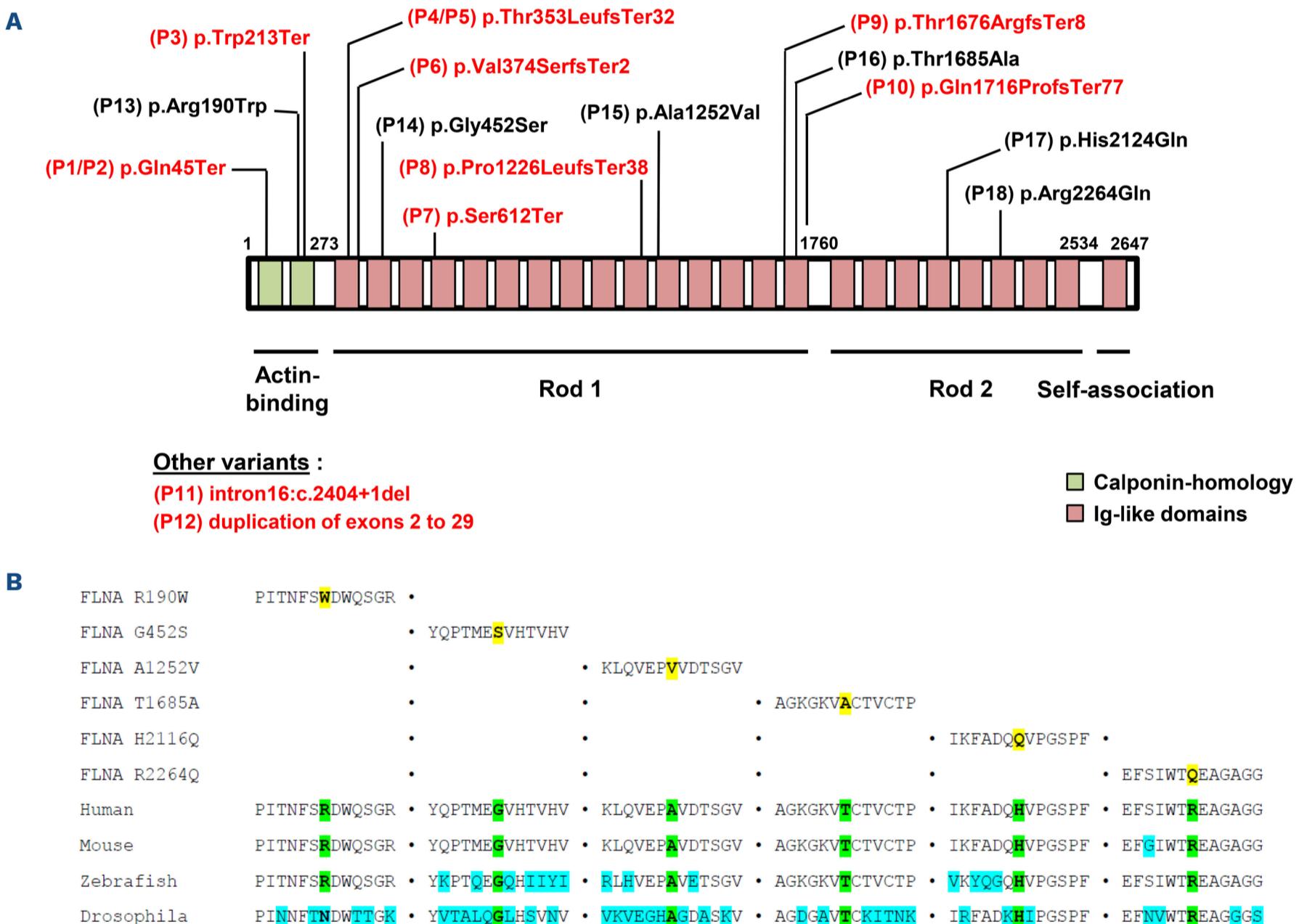
Ten variants were classified as null (12 patients), including three nonsense, five frameshift, one high splice variant (c.2404+1del; patient 11, P11), and one large duplication of exons 2-29. All were classified as pathogenic according to the American College of Medical Genetics (ACMG) guidelines (*Online Supplementary Table S1*).<sup>9</sup>

Patients carrying null variants displayed the classical filaminopathy phenotype (Table 1). Cardiac and vascular defects were common (N=9/12), including valvular malformations, persistent ductus arteriosus (PDA), aortic aneurysms, and venous insufficiency. Digestive disorders (N=3/12), such as malrotation and chronic intestinal pseudo-obstruction (CIPO), along with respiratory disorders (N=2/12), including emphysema and severe asthma, were also observed. Two patients reported hyperlaxity. Neurological features were prominent. Brain magnetic resonance imaging (MRI) was performed in all but P9, although she had seizures. MRI revealed PNH in 10 patients, a hallmark of filaminopathy, as other causes are anecdotal.<sup>4</sup> P12 had a distinctive neurological profile. This male patient, carrying a large *FLNA* duplication, exhibited brain MRI abnormalities (severe demyelination, hydrocephaly) but no PNH or neurological symptoms. Seven patients had epilepsy, and 4 experienced learning disabilities or mood disorders. This highlights the importance of brain MRI in suspected *FLNA*-related thrombocytopenia, even in asymptomatic cases.

From a hematological perspective, all patients had mild to moderate thrombocytopenia (50-150 G/L), with 3 exhibiting large or giant platelets (*Online Supplementary Figure S1*). Hemorrhagic manifestations were predominantly mucocutaneous, particularly easy bruising and abnormal uterine bleeding, as well as provoked bleeding during hemostatic challenges (mainly postpartum hemorrhage). Evaluation using the International Society on Thrombosis and Hemostasis Bleeding Assessment Tool (ISTH-BAT) indicated mild bleeding symptoms in most cases, with scores generally

below or near the established diagnostic thresholds ( $\geq 4$  for males,  $\geq 6$  for females and  $\geq 3$  for children).<sup>10</sup> These findings corroborate the previous reports,<sup>4,11</sup> although hematologic aspects were often overlooked, making this the largest study of *FLNA* variants associated with bleeding disorders. Intra-platelet *FLNA* was assessed in 6 patients using FCM (N=6) and IF (N=1) (Figure 2). Among female patients, two distinct platelet subpopulations were identified: *FLNA*-positive and *FLNA*-negative, with *FLNA*-negative platelets ranging from 25% to 75%. A proportion below 50% suggests shorter half-life of *FLNA*-positive platelets.<sup>11</sup> Two patients exhibited *FLNA*-negative platelets exceeding 50%, possibly due to variable X chromosome inactivation. P12, the only male of the cohort carrying a null variant (exon 2-29 duplication), dis-

played exclusively *FLNA*-negative platelets, consistent with full impairment of his single *FLNA* allele. Despite a typical phenotype (mild macrothrombocytopenia, CIPO, PDA, aortic aneurysm), P12 lacked epilepsy and PNH on MRI, but showed microbleeds, demyelination, and ventricular dilatations, reflecting the heterogeneous presentation of filaminopathy A,<sup>12</sup> particularly in males with potential mosaicism.<sup>13</sup> Therefore, screening for filaminopathy is recommended for males. FCM findings align with IF data (Figure 2B), supporting prior IF studies.<sup>4,6,14</sup> Both FCM and IF confirmed that *FLNA*-negative platelets are larger than *FLNA*-positive ones (*Online Supplementary Figure S2*). *FLNA*-deficient megakaryocytes prematurely release large, fragile platelets.<sup>11</sup> By providing quantitative data, FCM constitutes a valuable approach for



**Figure 1. Filamin A protein structure and variants analysis.** (A) Domains of the protein and studied variants of the cohort. Filamin A (*FLNA*) is a large dimeric actin-binding protein, each monomer consisting of 2646 amino acids (280 kDa). Its structure consists of two calponin homology sequences forming the actin binding domain in the N-terminal, followed by 24 immunoglobulin-like (Ig-like) domain repeats (90-100 amino acids). Rod 1 domain is a linear arrangement of Ig 1 to 15 separated from Rod 2 domain by Hinge 1. Rod 2 is more compact as it is made up of Ig 16 to 23 working in pairs. This part of the protein contains most of the binding sites, leading to numerous interactions with different partners. It ends with Hinge 2 followed by Ig24, which represents the C-terminal part of the protein and allows the dimerization. The null *FLNA* variants are written in red, the missense variants are written in black. (B) Sequence alignment. The amino-acid sequence of human *FLNA* protein was compared to orthologs using Clustal OMEGA (<http://www.ebi.ac.uk/Tools/msa/clustalo/>). The missense variants reported in this study alter the residues Arg190, Gly452, Ala1252, Thr1685, His2124 and Arg2264. The table gives the corresponding residue in three other species (mouse, zebrafish and drosophila).

**Table 1.** Clinical and biological features of the 18 patients included in the analysis.

Null variants*	Age at diagnosis years	Haematological				Neurological		Cardiovascular	Pulmonary involvement	Gastro-intestinal	Other
		Platelet count x10 <sup>9</sup> /L, mean (range)	Large/Giant platelets** %	Platelet dysfunction***	ISTH-BAT score****	Brain MRI	Clinical				
P1 (F) c.133C>T	29	111 (110-130)	10 / 2	No	6	PNH	Epilepsy Learning disabilities Mood disorders	Bicuspid aortic valve Mitral dysplasia	0	0	Spinal anomalies Retro-auricular fistula Alopecia
P2 (F) c.133C>T	31	71 (50-80)	A few / 0	Yes	1	PNH	Epilepsy Learning disabilities Mood disorders	Patent ductus arteriosus Aortic regurgitation Dilated ascending aorta Varicous vein	0	Common mesentery	Retro-auricular fistula
P3 (F) c.639G>A	48	99 (97-104)	NA	NA	NA	PNH	0	Patent ductus arteriosus	0	0	0
P4 (F) c.1056delG	42	118 (106-125)	0 / 0	Yes	4	PNH	Epilepsy	Aortic regurgitation Dilated ascending aorta Varicous vein	0	0	Hyperlaxity Raynaud Hashimoto Strabism
P5 (F) c.1056delG	8	120 (114-130)	10 / 4	Yes	1	PNH	Epilepsy Learning disabilities Mood disorders	Dysplastic aortic valve Aortic regurgitation	0	Chronic interstitial gastritis	Hyperlaxity Strabism
P6 (F) c.1120_1125delinsTCTTG	24	149 (133-169)	5 / 0	No	3	PNH	Epilepsy Learning disabilities Mood disorders	Atrial and ventricular septal defects Mitral and aortic regurgitations Dilated ascending aorta	Emphysema Obstructive ventilatory defect	0	Hyperlaxity
P7 (F) c.1835C>A	7	156 (148-165)	0 / 0	No	3	PNH	0	Dilated aorta	0	0	0
P8 (F) c.3677_3684del	NA	144	NA	NA	NA	PNH	0	Dilated aorta	0	0	0
P9 (F) c.5027_5030del	22	134	NA	Yes	2	NA	Epilepsy	0	Emphysema Severe asthma Pneumo-thorax	0	0

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Null variants*	Age at diagnosis years	Haematological				Neurological		Cardiovascular	Pulmonary involvement	Gastro-intestinal	Other
		Platelet count x10 <sup>9</sup> /L, mean (range)	Large/Giant platelets** %	Platelet dysfunction***	ISTH-BAT score****	Brain MRI	Clinical				
P10 (F) c.5146dup	55	119 (116-122)	8 / 3	Yes	3	PNH	Epilepsy	NA	NA	0	0
P11 (F) c.2404+1del	37	114 (102-129)	0 / 0	Yes	2	PNH	0	NA	NA	0	0
P12 (M) Duplication of exons 2 to 29	14	95 (60-125)	A few / 0	No	2	Demyelination Ventricular dilatations	0	Patent ductus arteriosus Aortic aneurysm Dissection of the iliac artery	0	CIPO	Abnormal erythrocyte morphology
<b>Missense variants*</b>											
P13 (F) c.568C>T	44	266 (232-295)	3 / 0	Yes	10	Normal	0	Mitral and aortic regurgitations	0	0	Miscarriages
P14 (F) c.1354G>A	30	134 (124-152)	3 / 0	No	6	Normal	0	0	Asthma	0	0
P15 (F) c.3755C>T	13	31 (22-78)	A few / 0	No	3	NA	0	0	Restrictive ventilatory defect Lung diffusion impairment	Hepatopathy	Hyperlaxity Anti-thyroid antibodies Pancytopenia
P16 (F) c.5053A>G	21	141 (130-162)	12 / 1	Yes	4	NA	NA	NA	0	0	0
P17 (F) c.6372C>G	32	98	4/0	No	0	NA	NA	0	0	0	Miscarriages
P18 (M) c.6791G>A	13	60	50 / 2	No	2	Normal	NA	Left ventricular compaction	0	0	Dental agenesis

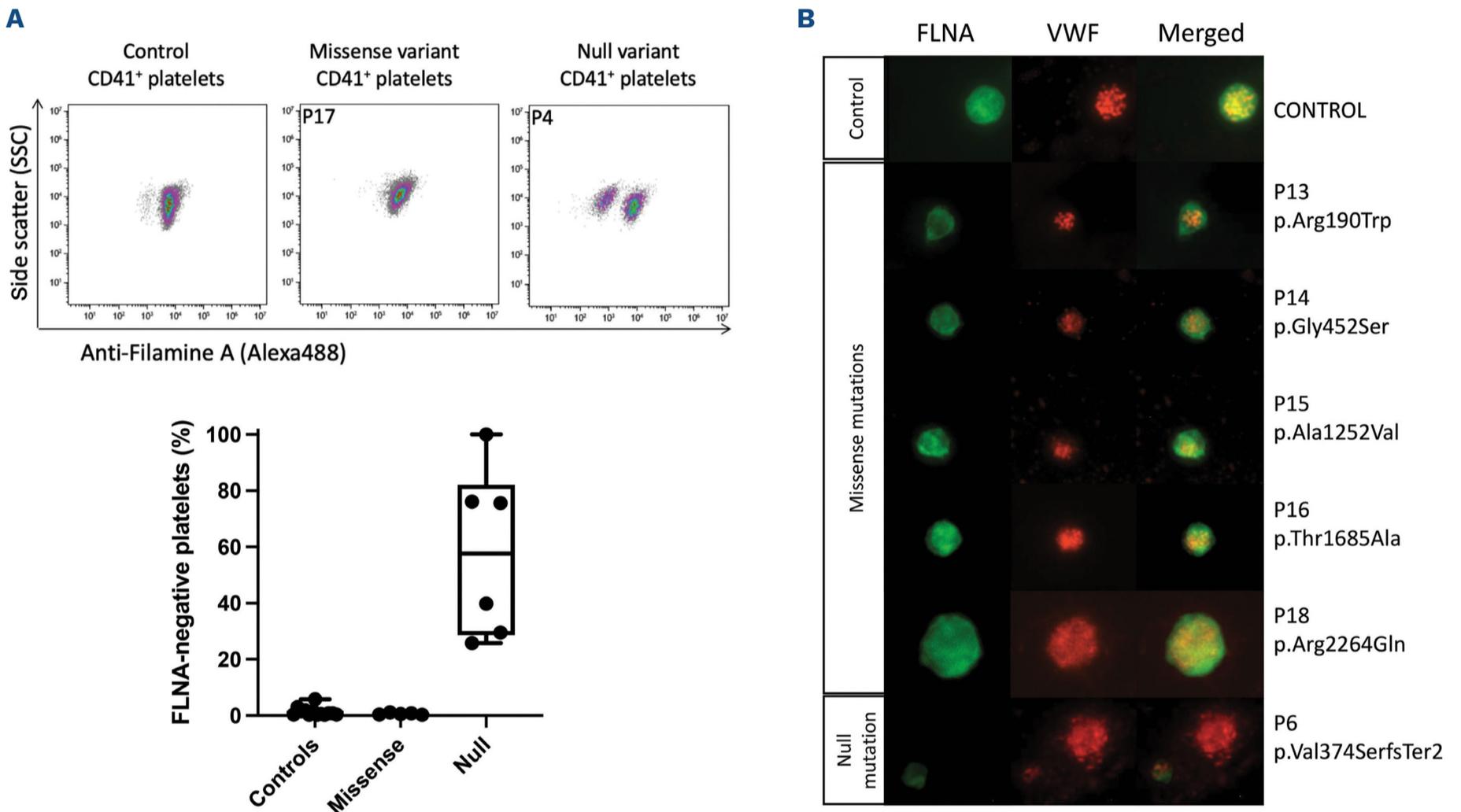
Clinical and biological data were retrospectively collected from patients referred to the French reference center of hereditary platelet disorders who were found to have either a null or a missense *FLNA* variant using a high-throughput sequencing panel targeting genes associated with constitutional platelet diseases. Patients P1 to P12 have null *FLNA* variants, while patients P13 to P18 have missense *FLNA* variants. Nodular periventricular heterotopia (PNH) was assessed using magnetic resonance imaging (MRI). \*All null variants were classified as ACMG class 5, and all missense variants as ACMG class 3. \*\* Large platelets are defined as platelets with a diameter equal or larger than half the diameter of an erythrocyte, and giant platelet are defined as platelets with a diameter equal or larger than the size of an erythrocyte. The proportions of large and giant platelets are <10% and <1% in healthy individuals, respectively.<sup>21</sup> \*\*\*Light transmission aggregometry was performed in P1, P2, P4, P5, P6, P7, P11, P12, P13, P14, P15, P16, P17 and P18. TME was performed in P13. PFA-100 was performed in P1, P2, P4, P5, P7, P9, P10, P11, P13, P14, P15 and P16. Platelet granule release assay was performed in P1, P2, P4, P5, P6, P9, P13, P14, P15 and P16. Mepacrine uptake and release assay was performed in P1, P2, P4, P5, P7, P11, P12, P13, P14, P15, P16 and P18. Intraplatelet serotonin was performed in P1, P2, P4, P5, P6, P9, P13, P14, P15 and P16. Flow cytometry analysis of platelet membrane glycoproteins was performed in P1, P2, P4, P5, P7, P11, P12, P13, P14, P15, P16 and P18. Intraplatelet plasminogen activator inhibitor-1 (PAI-1) quantification was performed in P1, P2, P4, P5, P6, P9 and P16. \*\*\*\*The international society on thrombosis and hemostasis – bleeding assessment tool (ISTH-BAT) score at diagnosis was obtained either by retrospectively calculating it from bleeding histories documented in patient records or by directly using scores previously assessed and recorded by the hematologists managing the patients. The accepted normal score ranges vary according to sex and age: 0-3 for males (M), 0-5 for females (F), and 0-2 for children. ADP: adenosine diphosphate; CIPO: chronic intestinal pseudo-obstruction; F: female; M: male; MPV: mean platelet volume; NA: not available; TRAP: thrombin receptor activator peptide.

diagnosing thrombocytopenia caused by *FLNA* null variants. It also provides a functional method for classifying intronic splicing variants. Intraplatelet quantification may serve as an early screening tool for constitutional thrombocytopenia, supporting filaminopathy diagnosis before genetic confirmation or clinical complications arise.

The other six variants were missense and classified as variants of “uncertain significance” (class 3 using ACMG guidelines). Predicted deleterious by multiple bioinformatic tools, they were absent or rare in general population da-

tabases (GnomAD) (*Online Supplementary Table S1*). They affected nucleotides conserved across species (human, mouse, zebrafish, drosophila), with three located in highly conserved regions (Figure 1B).

Patients carrying missense variants had mild to moderate thrombocytopenia (50-120 G/L) or even a normal platelet count (P13). Large or giant platelets were observed in 2 patients (*Online Supplementary Figure S1*). Their overall clinical picture was complex (Table 1), including bleeding manifestations (N=4/6), cardiac malformations (N=2/6), lung



**Figure 2. Evaluation of intraplatelet Filamin A.** (A) Quantification of intraplatelet Filamin A (FLNA) with flow cytometry measurement. Whole blood samples (100  $\mu$ L) anticoagulated with ethylenediaminetetraacetic acid (EDTA) were initially fixed using paraformaldehyde to a final concentration of 1% (vol/vol) for 10 minutes (min). Subsequently, centrifugation at 1000 g for 5 min at room temperature was performed. The cell pellet was then resuspended in a permeabilization buffer consisting of PBS with 2 mM EDTA, 0.5% BSA, and 0.5% Triton X-100 to ensure adequate permeabilization. The following day, 10  $\mu$ L of the fixed and permeabilized cells were stained for 15 min with antibodies against CD41 (CD41 APC, BD 559777 clone HIP8) and FLNA (C-ter) (FLNA A488, ab246749, epitope located within the final 100 amino acids of the protein) at room temperature. Finally, 200  $\mu$ L of PBS was added to the samples prior to FCM analysis to evaluate the expression of the target proteins. (Top) Representative cytometric analysis of a control subject and 2 patients, one carrying a missense variant (P17, p.His2124Gln) and one carrying a null variant (P4, p.Thr353LeufsTer32). (Bottom) Boxplots represent the percentage of FLNA-negative platelets obtained with FCM for the control group (N=13), the patients carrying a missense variant (N=5), and those carrying a null variant (N=6). All patients with a null variant exhibited FLNA-negative platelets, ranging from 25% to 100%. In contrast, all platelets from the control subjects and from patients with a missense variant expressed FLNA. (B) Evaluation of intraplatelet FLNA with immunofluorescence. Fluorescence microscopy analysis comparing the distribution of FLNA and von Willebrand Factor (VWF) in fixed cells from 6 patients and one healthy control. Cells were fixed with pre-cooled methanol for 1 min at  $-20^{\circ}\text{C}$  and washed three times with Phosphate Buffered Saline (PBS) containing 0.5% Bovine Serum Albumin (BSA). A 30-min incubation with PBS:0.5% BSA was undertaken as a blocking procedure. The primary antibodies, mouse anti-filamin A (sc-71118, 1:50) and rabbit anti-VWF (Dako, 1:500), were incubated at room temperature for 1-2 hours, followed by three PBS washes. Secondary antibodies, anti-mouse Alexa Fluor 488 (A11029, Invitrogen, 1:500) and anti-rabbit Alexa Fluor 546 (A11010, Invitrogen, 1:500), were subsequently applied, and cells were incubated in a light-free environment. Following a further three washes in PBS, the samples were mounted with Fluoromount containing 4',6-diamidino-2-phenylindole (DAPI) for analysis via fluorescence microscopy. Merged panel: P6 (c.1120\_1125delinsTCTTG – p.Val374SerfsTer2) showed 2 subtypes of platelets: FLNA-negative large platelet and FLNA-positive normal size platelet. Note that P18 (c.6791G>A – p.Arg2264Gln) presented FLNA-positive large platelets.

disorders (N=2/6), hyperlaxity (N=1/6), and autoimmune disorders. Notably, no seizures or PNH were observed, although only 3 patients underwent brain MRI. Several PNH cases with a missense *FLNA* variant have been reported,<sup>15</sup> but data on the variants' pathogenicity and platelet count were lacking. Intra-platelet *FLNA* study using FCM (N=5) and IF (N=5) showed no *FLNA*-negative platelets (Figure 2), suggesting thrombocytopenia might result from qualitative rather than quantitative *FLNA* defect, or may even be independent of *FLNA*. Further functional assays are needed to elucidate the impact of these missense variants. In P15 and P16, genetic analyses identified alternative molecular etiologies for their hematological phenotype. P15 had a genetically confirmed telomeropathy (two heterozygous "likely pathogenic" variants in *TERT*, p.Ser12Phe, and p.Phe560Leu). P16 had an *ACTN1*-related thrombocytopenia ("likely pathogenic" variant p.Arg738Gln).<sup>16</sup> Although these alternative genetic causes satisfy BP5 criteria from the ACMG guidelines, they are insufficient to reclassify *FLNA* variants as "likely benign". However, they suggest that the *FLNA* variant is unlikely to be the primary cause of thrombocytopenia in these cases. P13, the only patient in the cohort with a normal platelet count, despite mucocutaneous hemorrhage and provoked bleeding, had no alternative molecular diagnosis. However functional platelet studies revealed a dense granule deficiency, potentially explaining the bleeding tendency. P17 carried an *ACTN1* variant of "uncertain significance" (p.Ala587Val), which could explain the disease as plausibly as the *FLNA* variant. Genetic investigations and routine functional studies did not identify any other etiology for thrombocytopenia in P14 and P18. Structural studies provided further insights. Cryo-electron microscopy of the actin-binding domain complex showed binding within the calponin-homology 1 (CH1) domain (Lys43-Ser149).<sup>17</sup> Variant P13 (p.Arg190Trp) in CH2 (Gln166-Leu269), lies outside actin-binding sequences, supporting the alternative diagnosis of dense granule deficiency. Variant P14 (p.Gly452Ser) and P16 (p.Thr1685ala), may impact the protein's folding (protein stability free energy change ( $\Delta\Delta G$ ) -0.179 and -0.069 kcal/mol, respectively), possibly affecting its stability. In contrast, P17 (p.His2124Gln), had a slight stabilizing effect ( $\Delta\Delta G$  0.044 kcal/mol). This variant lies within the GPIIb $\alpha$ -binding domain, deletion of which has shown no significant impact on proplatelet formation *in vitro*.<sup>18</sup> Variant P15 (p.Ala1252Val) affects Ig-like domain 11 in a loop connecting it to Ig-10, without clear structural implication, supporting the alternative diagnosis of telomeropathy. Variant P18 (p.Arg2264Glu) is near the  $\beta 3$  C-terminal binding site of  $\alpha IIb\beta 3$  integrin (*Online Supplementary Figure S3*). Modeling within conformer 16 of the Ig21- $\alpha IIb\beta 3$  C-terminal complex nuclear magnetic resonance (NMR) structure showed a disruptive  $\Delta\Delta G$  of 1.01 kcal/mol. This variant may weaken *FLNA*- $\alpha IIb\beta 3$  interaction, which appears to play a crucial role in RhoA pathway downregulation,<sup>18</sup> thereby affecting actomyosin contractility and proplatelet formation. This study reports the clinical, genetic, and biological char-

acteristics of the largest cohort of filaminopathies A with hematological involvement. It highlights the importance of considering the type of *FLNA* variant and its association with specific clinical features. Thrombocytopenia is typically mild, large and giant platelets may be observed, and platelet function testing reveals non-specific or even normal findings, making the platelet phenotype insufficiently distinctive on its own. The presence of PNH on brain MRI and *FLNA*-negative platelets are strong indicators of *FLNA*-related thrombocytopenia and may constitute an effective screening method for diagnosis as suggested by previous reports.<sup>4,14,19,20</sup> The causal role of missense variation was ruled out in 3 out of the 6 cases indicating that, in the absence of PNH, caution should be exercised when interpreting this type of variation. Further research is needed to better understand the contribution of missense variants to *FLNA*-related thrombocytopenia.

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**Disclosures**

No conflicts of interest to disclose.

**Contributions**

MF, SB, CG, MY, J-BV, NH, CF, MI-K, ML and M-CA performed the clinical and biological characterization of patients; VS and MP

performed the functional experiments; PS, MI-K, MP and M-CA conceived and supervised the project; JV-A performed the structural analysis of the protein; CB and PS analyzed the data and wrote the manuscript.

**Data-sharing statement**

The dataset generated and analyzed is available from the corresponding author on request.

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