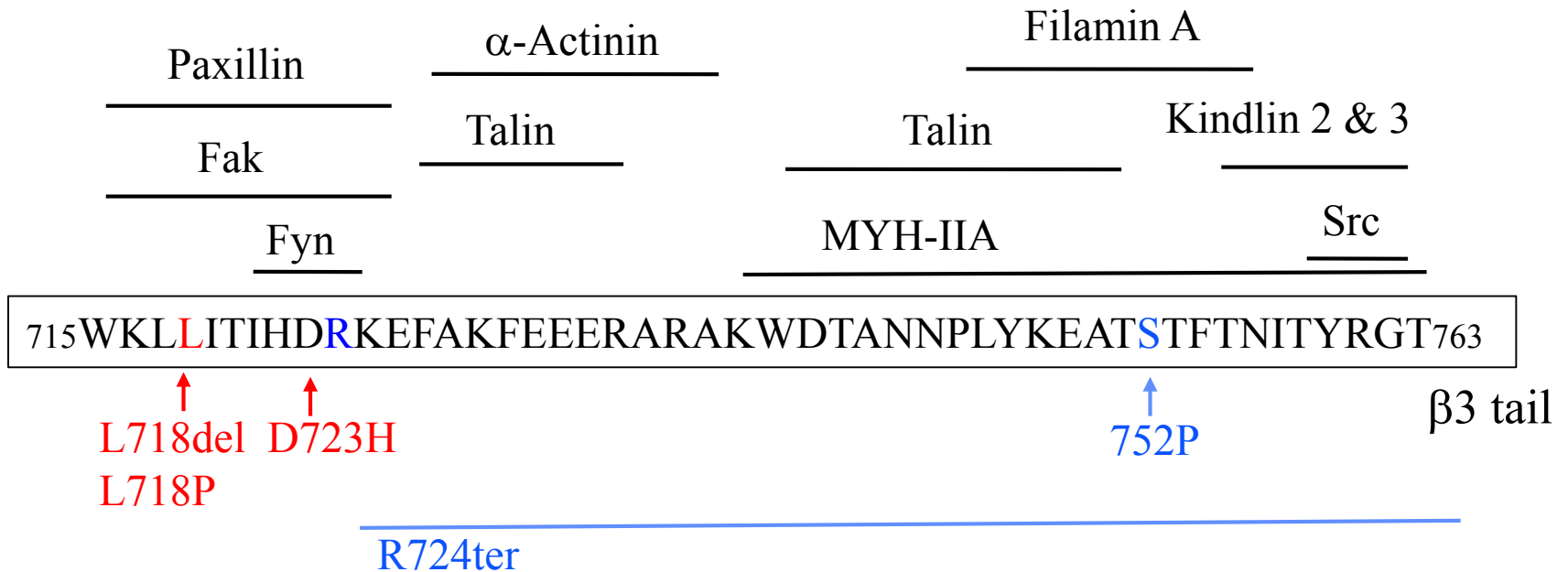


**Fig. S1**

$\beta$ 3 cytoplasmic tail: functional domains



$\beta$ 3 cytoplasmic tail: genetic variants

**MTP +/- Altered function**  
**Altered function only**

References for the  $\beta$ 3-binding domain assignment for the proteins highlighted in Suppl Fig. 1.

### Talin

Wegener KL, Partridge AW, Han J, Pickford AR, Liddington RC, Ginsberg MH, Campbell ID. Structural basis of integrin activation by talin. *Cell*. 2007; 128(1):171-182

### Kindlin 2&3

Moser M, Nieswandt B, Ussar S, Pozgajova M, Fassler R. Kindlin-3 is essential for integrin activation and platelet aggregation. *Nat Med* 2008;14(3):325-330

Xu Z, Chen X, Zhi H, Gao J, Bialkowska K, Byzova TV, Pluskota E, White GC II, Liu J, Plow EF, Ma Y-Q. Direct interaction of kindlin-3 with integrin  $\alpha$ IIb $\beta$ 3 in platelets is required for supporting arterial thrombosis in mice. *Arterioscler Thromb Vasc Biol* 2014; 34:1961-1967.

### Src

Wu Y, Span LM, Nygren P, Zhu H, Moore DT, Cheng H, Roder H, DeGrado WF, Bennett JS. The tyrosine kinase c-Src specifically binds to the active integrin  $\alpha$ IIb $\beta$ 3 to initiate outside-in signaling in platelets. *J Biol Chem* 2015; 290(25):15825-34.

### Fyn

Legate KR, Fassler R. Mechanisms that regulate adaptor binding to beta3-integrin cytoplasmic tails. *J Cell Science* 2009; 122(2):187-98.

### MYH-IIA

Jenkins AL, Nannizzi-Alaimo L, Silver D, Sellers JR, Ginsberg MH, Law DA, Phillips DR. Tyrosine phosphorylation of the beta3 cytoplasmic domain mediates integrin-cytoskeletal interactions. *J Biol Chem* 1998; 273(22):13878-13855.

### Filamin A

Liu J, Das M, Yang J, Ithychanda SS, Yakubenko VP, Plow EF, Qin J. Structural mechanism of integrin inactivation by filamin. *Nat Struct Mol Biol* 2015; 22:383-9.

### Paxillin and Fak (may be indirect via an adaptor protein)

Schaffner-Reckinger E, Gouon V, Melchior C, Plançon S, Kieffer N. Distinct involvement of beta3 integrin cytoplasmic domain tyrosine residues 747 and 759 in integrin-mediated cytoskeletal assembly and phosphotyrosine signaling. *J Biol Chem* 1998; 273(20):12623-32.

### Alpha-actinin

Legate KR, Fassler R. Mechanisms that regulate adaptor binding to beta3-integrin cytoplasmic tails. *J Cell Science* 2009; 122(2):187-98.

**Table S1:** A/ Published data for previously reported intracellular domain mutations of  $\beta 3$  giving MTP

Publication	Ghevaert et al (ref 14)	Gresele et al, (ref 15)	Kashiwagi et al, (ref 16)	Jayo et al (ref 17)	Kobayashi et al, (ref 18)
Mutation	$\beta 3$ -D723H	$\beta 3$ (D621_E660del)	$\beta 3$ (D621_E660del)	$\beta 3$ -L718P	$\beta 3$ -L718P
Platelet count and volume	MTP	MTP	MTP	TP and platelet anisocytosis	TP and platelet anisocytosis
Expression of $\alpha$ Ib $\beta$ 3 at the platelet surface	Reduced	Mild reduction	Reduced (67%)	Modest reduction	Reduced (45-75%)
Platelet aggregation	Normal	Impaired	Not detailed	Much reduced	Much reduced
$\alpha$ Ib $\beta$ 3 activation (PAC-1 bindingf)	Modest binding of PAC-1, normal after activation	Weak spontaneous binding of PAC-1, decreased (50%) after activation	Modest spontaneous binding of PAC-1	Spontaneous binding of PAC-1*, much reduced to activated platelets	Some spontaneous binding of PAC-1, much decreased after activation
Genetic transmission	AD	AD	AD	Isolated case	AD
Severity of the bleeding syndrome	Mild	Moderate/severe	Moderate (few details)	Severe	Mild bleeding

TP, thrombocytopenia; MTP, macrothrombocytopenia; AD, autosomal dominant; \* after transfection

B/ List of genes involved in macrothrombocytopenia (Savoia A, Curr Opin Hematol 2016; 23:486-492) or abnormal  $\alpha$ -granules and for whom

no potential causal mutations were identified by whole exome sequencing. *FLII*, *ACTN1*, *GFI1B*, *PKACG*, *FLNA*, *ETV6*, *MYH9*, *DIAPH1*, *TRPM7*, *SLFN14*, *GP1BA*, *GPIBB*, *GP9*, *RUNX1*, *GATA1*, *SRC*, *VPS33*, *VIPA39*, *NBEAL2*.