



## Gain-of-Function Mutation in Filamin A Potentiates Platelet Integrin $\alpha\beta$ Activation

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Titre Gain-of-Function Mutation in Filamin A Potentiates Platelet Integrin  $\alpha\beta$  Activation

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**OBJECTIVE:** Dominant mutations of the X-linked filamin A ( ) gene are responsible for filaminopathies A, which are rare disorders including brain periventricular nodular heterotopia, congenital intestinal pseudo-obstruction, cardiac valves or skeleton malformations, and often macrothrombocytopenia.

**APPROACH AND RESULTS:** We studied a male patient with periventricular nodular heterotopia and congenital intestinal pseudo-obstruction, his unique X-linked allele carrying a stop codon mutation resulting in a 100-amino acid-long FLNa C-terminal extension (NP\_001447.2: ). Platelet counts were normal, with few enlarged platelets. FLNa was detectable in all platelets but at 30% of control levels. Surprisingly, all platelet functions were significantly upregulated, including platelet aggregation and secretion, as induced by ADP, collagen, or von Willebrand factor in the presence of ristocetin, as well as thrombus formation in blood flow on a collagen or on a von Willebrand factor matrix. Most importantly, patient platelets stimulated with ADP exhibited a marked increase in  $\alpha\beta$  integrin activation and a parallel increase in talin recruitment to  $\beta$ , contrasting with normal Rap1 activation. These results are consistent with the mutant FLNa affecting the last step of  $\alpha\beta$  activation.

Overexpression of mutant FLNa in the HEL megakaryocytic cell line correlated with an increase (compared with wild-type FLNa) in PMA-induced fibrinogen binding to and in talin and kindlin-3 recruitment by  $\alpha\beta$ .

**CONCLUSIONS:** Altogether, our results are consistent with a less binding of mutant FLNa to  $\beta$  and the facilitated recruitment of talin by  $\beta$  on platelet stimulation, explaining the increased  $\alpha\beta$  activation and the ensuing gain-of-platelet functions.

Résumé en anglais

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