# The GPIIb-IIIa defect of platelets in Glanzmann thrombasthenia

Alan T. Nurden

Institut Hospitalo-Universitaire LIRYC, Pessac, France

E-mail: nurdenat@gmail.com

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| **TITLE** | An abnormal platelet membrane glycoprotein pattern in three cases of Glanzmann's thrombasthenia. |
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Eduard Glanzmann was a Swiss pediatrician who in 1918 reported an inherited platelet functional disorder associated with a defective clot retraction. The clinical phenotype of this autosomal recessive bleeding disorder, later known as Glanzmann thrombasthenia (GT), was largely defined in the 1960s with major contributions from Jacques Caen in Paris and Marjorie Zucker in New York. My involvement in platelet research began in Oxford in 1968. Our project at that time was to define the components of the platelet "glycocalyx", a carbohydrate-rich layer first highlighted on platelets by an electron microscopist, Olaf Behnke, in Copenhagen. I applied cytochemical techniques to identify negatively charged elements digested from this surface layer and separated by polyacrylamide gel electrophoresis (PAGE). Use of the detergent sodium dodecyl sulfate (SDS) and SDS-PAGE soon enabled the separation of the major intrinsic membrane glycoproteins (GP). Teams led by Ralph Nachman (New York) and David Phillips (Memphis) highlighted three major bands termed GPI (a sialic acid rich GP), GPII and GPIII. I continued my research in London and identified these GP in a range of mammals. However, I quickly realized that inherited platelet disorders held the key to identifying their function.

Early in 1973, I visited Jacques Caen in Paris to apply electrophoretic procedures to the platelets of his patients. How well I remember looking long and hard at my first carbohydrate-stained SDS-PAGE gels. I realized that, for each patient investigated, while the acidic GPI was present, the GPII and GPIII bands were hardly to be seen. The results were published in the British Journal of Haematology in 1974[1] and confirmed in Nature in 1975.[2] A single dimension tube gel from a patient with Glanzmann thrombasthenia is shown in Figure 1. Meanwhile, on the other side of Paris, David Phillips and his co-workers were independently studying the surface topography of GT platelets using lactoperoxidase-catalyzed iodination ($^{125}$I) and in 1975 they published similar results to ours, also in Nature.[3]

As the complexity of the platelet surface constituents evolved, so did the nomenclature, and the affected GP became known as GPIIb and GPIIIa. Studies in my group,

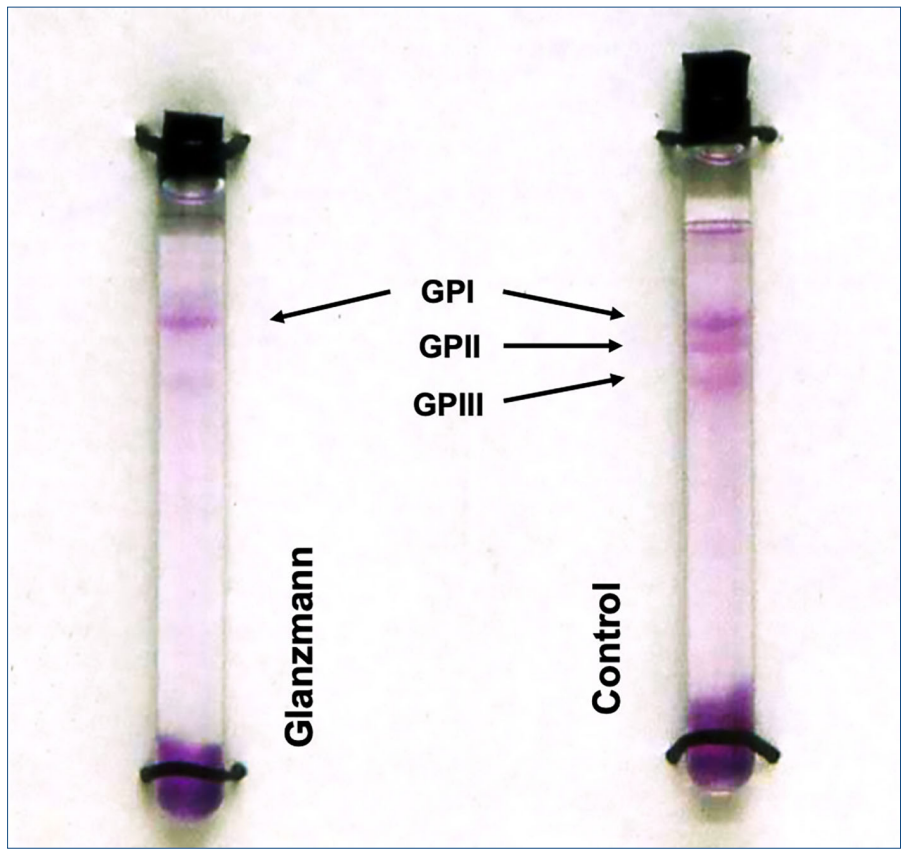


**Figure 1. The discovery of the glycoprotein IIb and glycoprotein IIIa defects in platelets in a patient with Glanzmann thrombasthenia.** Sodium dodecyl sulfate (SDS)-soluble platelet proteins were separated by SDS-polyacrylamide gel electrophoresis on single dimension tube gels prior to carbohydrate staining. Whereas the major glycoprotein I (GPI) band was clearly seen, the GPII and GPIII bands were absent or barely visible. (Figure adapted with permission from Nurden *et al.* Br J Haematol 1974)

first with Inger Hagen from Oslo and then with Tom Kunicki from Milwaukee, showed that, in fact, GPIIb and GPIIIa formed a $Ca^{2++}$-dependent complex in the normal platelet membrane; a complex soon identified as the αIIbβ3 integrin. James George (Oklahoma) and Uri Seligsohn (Tel Aviv) were major contributors in promoting a greater understanding of the clinical aspects of GT. The role of αIIbβ3 as a fibrinogen receptor responsible for aggregation and clot retraction was progressively defined, while the nature of the mutations within the genes *ITGA2B* (encoding αIIb) and *ITGB3* (encoding β3) gave rise to the classic and variant forms of GT that are now used around the world as part of the diagnostic procedure.[4] Pioneers in the early studies included Peter Newman (Milwaukee), Mark Ginsberg (La Jolla), Gerard Marguerie (La Jolla and Paris), Edward Plow (La Jolla), Joel Bennett (Philadelphia), Sandford Shattil (La Jolla), and Paul Bray (Baltimore), while a special mention goes to Barry S. Coller (New York), among many others.

**Disclosure**

*No conflicts of interest to disclose.*

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