Glanzmann's Thrombasthenia is a rare inherited bleeding disorder caused by a deficiency or dysfunction of the GPIIb-IIIa receptor on platelets. Glanzmann's thrombasthenia was first identified in 1918 by Dr. Glanzmann, in children from a village in the Swiss Alps. Glanzmann's Thrombasthenia has an incidence of about 1/1,000,000 but is more common in populations where marriage between blood relatives is common.

**Pathology**

Glanzmann's Thrombasthenia is characterised by abnormalities in either GPIIb or GPIIIa resulting in loss of GPIIb/IIIa receptor function. The platelet GPIIb-IIIa receptor is required for platelet aggregation. Abnormalities of the receptor provoke a profound defect in platelet aggregation and secondary defects in platelet adhesion and platelet coagulant activity; therefore result in a failure of platelet plug formation at sites of vascular injury, leading to excessive bleeding and bruising.

The GPIIb-IIIa receptor is also responsible for the uptake of fibrinogen from plasma into platelet α granules, so patients with Glanzmann's Thrombasthenia have markedly reduced levels of platelet fibrinogen. In addition, clot retraction also requires platelets with intact GPIIb-GPIIIa receptors, presumably to make contact with fibrin. So patients with Glanzmann's Thrombasthenia usually have abnormal clot retraction.

**Inheritance**

The gene for GPIIb-IIIa is carried on chromosome 17 in humans, one of the 22 pairs of autosomal chromosomes, so it affects men and women equally.

**Laboratory tests**

Patients with Glanzmann's Thrombasthenia have normal platelet counts and morphology, prolonged bleeding times, decreased or absent clot retraction, and abnormal platelet aggregation responses to physiologic stimuli. Platelets of patients with Glanzmann's Thrombasthenia have a normal initial slope of ristocetin-induced aggregation, reflecting the normal levels of plasma von Willebrand factor and the normal platelet GPIb/IX content; the reduced second wave of aggregation at low doses of ristocetin reflects the impaired GPIIb-IIIa function, and the interesting cyclical aggregation at higher doses of ristocetin probably reflects a complex interaction between ristocetin-induced binding of von Willebrand factor to GPIb/IX and inhibition of this interaction by released ADP. In each case, the abnormalities reflect the inability of the platelets to bind fibrinogen and/or other adhesive glycoproteins.
Glanzmann's thrombasthenia is classified into three types, depending on the level of GPIIb-IIIa present:

- **Type 1 (severe):** <5% of normal GPIIb-IIIa levels.
- **Type 2 (less severe):** 10-20% of normal GPIIb-IIIa levels.
- **Type 3 (variant):** normal levels of GPIIb-IIIa, but functionally inactive.

The clinical severity of Glanzmann's Thrombasthenia does not correlate with the sub-type.

**Bleeding episodes**

Children with Glanzmann's Thrombasthenia are often diagnosed early in life, and often before the age of five, usually by unexplained spontaneous bleeding from mucous membranes. Purpura (bruising under the skin) is also very common, but not dangerous\(^1\). Bleeding episodes in people with Glanzmann's Thrombasthenia include: nose bleeds, easy bruising, gingival bleeding (during teething or losing baby teeth during childhood or even over-vigorous brushing), gastrointestinal bleeding, CNS haemorrhage, hematuria, muscle haematoma, haemarthrosis, menorrhagia. (often worse for their first period). Bleeding can also occur after major and minor surgical procedures (e.g.: circumcision, dental extraction etc). Glanzmann's thrombasthenia is rare and its clinical manifestations are similar to many other platelet function disorders. The patient's clinical history of bleeding disorders is very important for diagnosis.

**Current treatment options**

The goal of treatment for patients with FVII deficiency is to control bleeding episodes.

- **Platelet transfusion** is the standard therapy. However, approximately 15-30% of patients become refractory to platelet transfusion or develop antibodies to GPIIb-IIIa and/or HLA antibodies.

- **NovoSeven®** is indicated for the treatment of bleeding episodes and for the prevention of bleeding during surgery or invasive procedures in patients with Glanzmann's thrombasthenia with antibodies to GPIIb-IIIa and/or HLA, and with past or present refractoriness to platelet transfusions. The recommended dosage is 90 ug/kg bw (range 80-120ug) per kg bw by intravenous injection every 2 hours (range 1.5-2.5 hours). At least three doses should be administered to secure haemostasis. NovoSeven® has documented efficacy in Glanzmann's thrombasthenia patients with a wide range of bleeding episodes and in patients undergoing invasive/diagnostic procedures and/or surgery. NovoSeven® is free of human plasma and albumin, so there is no risk of
human viral transmission. Due to the low prevalence of patients with Glanzmann's thrombasthenia with platelet refractoriness, the clinical experience with NovoSeven® treatment is limited.

- **Other treatments:**
  
  - Compression, gelatine sponge or gauze, antifibrinolytic agents such as tranexamic acid or topical thrombin can be used to control minor bleeds. Nosebleeds may be controlled by packing the nasal cavity or with application of gel foam soaked in topical thrombin or YAG laser. However a vicious circle may develop with the packing irritating the nasal mucosa causing the bleed to start again when the packing is removed.
  
  - Desmopressin (DDAVP) has been tried in some patients with Glanzmann's Thrombasthenia and may shorten bleeding time in patients with type 2 only, but there is no notable clinical efficacy.
  
  - Oral contraceptives can regularise menstrual cycles and reduce the bleeding. This is sometimes recommended before a girl's first period, as haemorrhage is particularly severe at this time.
  
  - Immunoabsorption is the removal of antibodies to platelets by plasma exchange with the use of protein-A sepharose columns which may transiently restore platelet efficacy. However this technique is not available everywhere, it is labour intensive, and requires an adequate venous access. It is not of use in control of active bleeding as this process requires several hours.
  
  - Allogeneic marrow transplant has been reported in two patients with Glanzmann's thrombasthenia.