**GFI1B** mutation causes autosomal dominant gray platelet syndrome

**References**


A dominant-negative GFI1B mutation in the gray platelet syndrome.
Monteferrari, et al. (2014)

Gray platelet syndrome (GPS) or platelet alpha-granule deficiency, is a rare congenital autosomal bleeding disorder caused by defective alpha-granule production. This leads to a reduction or absence of alpha-granules in blood platelets, and the release of proteins normally contained in these granules into the marrow, causing myelofibrosis. GPS is caused by the failure of the megakaryocytes to package secretory proteins into alpha-granules (Fig. 3 – megakaryocytic pathway). It is usually characterized by thrombocytopenia and abnormally large agranular platelets in peripheral blood smears.

Approximately, 60 cases from various populations around the world have been described and the incidence is the same in males and females [http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=721]. Accessed 10/3/2014. GPS has two distinct forms including both autosomal recessive and autosomal dominant forms. The genetic cause of autosomal recessive GPS has been linked to biallelic NBEAL2 missense mutations (1–3). NBEAL2 encodes a protein that is expressed in platelets and megakaryocytes. This protein is required for the development of platelet alpha-granules. To date, no genes have been implicated in the autosomal dominant form.

Monteferrario and his colleagues identified a transcription-factor gene, growth factor independent 1B gene (GFI1B), as the causative gene for autosomal
dominant GPS. A non-sense mutation was detected in *GFI1B* that completely co-segregated with the disease in their linkage analysis, in a large family with autosomal dominant GPS. *GFI1B* encodes a transcriptional repressor that has been implicated in megakaryopoiesis. Molecular and functional analyses in affected patients reveal large gray platelets with reduced or no alpha granules, thrombocytopenia, mild myelofibrosis, reduced platelet factor 4 expression, megakaryocytes and platelets positive for the stem-cell and progenitor-cell marker CD34, abnormal distribution of megakaryocytes in the bone marrow and reduced expression of glycoprotein 1bα CD42B. Also, a dominant-negative inhibition of the non-mutant protein GFI1B transcriptional activity by GFI1B mutant protein was observed.

In conclusion, Monteferrario and his colleagues identified *GFI1B* as a causative gene in autosomal dominant GPS. This will provide the basis of a molecular genetic diagnosis. The molecular genetic diagnosis of autosomal dominant GPS will offer genetic counseling and expand the benefits of prenatal and pre-implantation-genetic diagnosis. These results also open new research avenues into the role of *GFI1B* in autosomal dominant GPS and the molecular pathways that are key for megakaryopoiesis and platelet production. Furthermore, a wide range of platelet disorders including GPS might be treated and managed by developing innovative therapeutic strategies that selectively target the *GFI1B* gene, the master regulator of megakaryocyte and platelet production. Furthermore, a wide range of platelet disorders including GPS might be treated and managed by developing innovative therapeutic strategies that selectively target the *GFI1B* gene, the master regulator of megakaryocyte and platelet production.

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