Familial platelet disorder with predisposition to acute myelogenous leukemia (FPD/AML)

Paula G Heller

Hematologia Investigacion, Instituto de Investigaciones Medicas Alfredo Lanari, Universidad de Buenos Aires, Unidad Ejecutora IDIM-CONICET, Combatientes de Malvinas 3150 Buenos Aires 1427, Argentina. (PGH)

Published in Atlas Database: July 2008

Online updated version: http://AtlasGeneticsOncology.org/Kprones/FamPlateletDisAMLID10079.html

DOI: 10.4267/2042/44528

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence. © 2009 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Alias
Familial platelet disorder with predisposition to myeloid malignancy

Inheritance
Familial platelet disorder with predisposition to acute myelogenous leukemia is a rare autosomal dominant disorder caused by heterozygous germline mutations in transcription factor RUNX1. Only fifteen pedigrees have been reported to date. The disease appears to have complete penetrance and affected individuals are born at the expected frequency for an autosomal dominant trait. There have been no reports of parental consanguinity among the pedigrees described so far, and males and females are equally affected. Together with CEBPA-associated leukemia and familial monosomy 7, FPD/AML represents one of the few identified genetic disorders underlying pure familial leukemia cases.

Clinics

Phenotype and clinics
Familial platelet disorder with predisposition to acute myelogenous leukemia is characterized by inherited thrombocytopenia, platelet function defect and a lifelong risk of myelodysplastic syndrome (MDS) and acute myelogenous leukaemia (AML). Thrombocytopenia is usually mild to moderate and is characterized by normal platelet size. Decreased expression of the thrombopoietin Mpl receptor has been found in these patients, providing a potential explanation for low platelet counts. Bleeding tends to be more severe than expected according to the degree of thrombocytopenia due to the presence of associated platelet dysfunction and results in a significant bleeding diathesis, which, although not severe, might be life-threatening after surgery or child-bearing. Platelet aggregation is abnormal in response to several platelet agonists although the mechanisms underlying this defect are not clear. Both platelet storage pool deficiency and impaired alpha IIb beta3 integrin (GPIIbIIIa) activation and fibrinogen binding have been described. The presence of platelet dysfunction seems to be a constant feature of this disorder and, although frequently associated to thrombocytopenia, some affected individuals display platelet counts at the lower limit of normal.

Neoplastic risk
Patients with FPD/AML are predisposed to myeloid malignancies, including AML and MDS. Several AML FAB subtypes have been reported to occur, including M1, M2, M4 and M5, while refractory anemia with excess blasts, chronic myelomonocytic leukemia and hypoplastic MDS with myelofibrosis have been described among the cases with MDS. The rate of myeloid malignancies ranges between 20 to 65% and peaks at the fourth decade of life. Median age of leukemia onset is 37 years old, ranging from 6 to 75. Germline RUNX1 mutations seem to be insufficient by themselves for leukemia development and acquisition of additional cooperating events are required. Several cytogenetic abnormalities have been identified in FPD/AML patients who develop myeloid neoplasms, including del(5q), -7/del(7q), +8, del(11q), 11q23.
rearrangements, del (20q) and +21. On the other hand, no mutations have been found in the remaining RUNX1 allele in FPD/AML patients who developed leukemia.

The mechanisms by which germline RUNX1 mutations predispose to leukemia remain unclear. RUNX1 deficiency in adult mice (RUNX1 +/- and -/-) is accompanied by an increase in committed myeloid progenitors, which could be explained by alteration in proliferative and/or self-renewal capacity or, alternatively, by partial block in differentiation. These abnormalities result in an expanded pool of progenitors susceptible to second mutations. Besides, there is evidence that RUNX1 functions as a tumor suppressor gene through up-regulation of p14ARF, which enhances p53 tumor-suppressive activity by binding to its negative regulator Mdm3. RUNX1 is believed to be haploinsufficient for tumor suppression, providing an additional explanation for leukemia predisposition seen in this disorder.

**Treatment**

Recommendations for management of FPD/AML patients are lacking due to the low frequency of this disorder and need to be assessed individually. Bleeding should be managed as for other platelet function disorders, according to severity of bleeding manifestations. Patients with FPD/AML who develop AML or MDS are candidates for hematopoietic stem cell transplantation. As thrombocytopenia in FPD/AML is frequently mild or moderate and may be overlooked, mutational screening of potential sibling donors is required to avoid transplantation of stem cells harbouring the same RUNX1 mutation.

**Prognosis**

Platelet counts tend to remain stable throughout lifetime except when development of myeloid malignancy occurs. Prognosis depends on disease transformation to MDS/AML, the risk of which seems to vary according to the type of RUNX1 mutation and its effect on RUNX1 function.

**Genes involved and proteins**

**RUNX1 (runt-related transcription factor 1)**

*Alias*

AML1 (acute myeloid leukemia 1)

CBFA2 (core-binding factor, alpha subunit 2)

*Location*

21q22.12

*DNA/RNA*

Description: The RUNX1 gene encompasses 12 exons. Exons 3 to 5 encode the DNA-binding domain, while the transactivation domain is enclosed in exons 7b and 8. Transcription yields several isoforms, which are generated by alternative splicing, different promoter usage and differential usage of polyadenylation sites. Most abundant species include isoforms RUNX1b and RUNX1c, which encode the full-length protein. Transcription of RUNX1c is initiated at the distal promoter and includes exons 1 and 2, while RUNX1b is regulated by the proximal promoter and starts at exon 3, both including exons 4, 5, 6, 7b and 8, according to nomenclature described by Miyoshi and colleagues. Thus, RUNX1b and c differ at their amino (N)-terminal end, being the former 27 amino acids shorter than the latter, although there appears to be no relevant functional differences between them. In contrast, the shorter RUNX1a isoform is a truncated variant spanning exons 3 to 7a with DNA-binding but no transactivation activity which may potentially interfere with RUNX1b and c function, acting as a negative regulator.

*Protein*

Description: The RUNX1b protein consists of 453 amino acids with 48 kDa molecular weight, RUNX1c comprises 480 amino acids while RUNX1a is formed by 250 amino acids. RUNX1 belongs to a family of heterodimeric transcription factors which include RUNX2 and RUNX3, all of them forming heterodimers with CBFbeta.

RUNX factors comprise an N-terminal region named the runt homology domain (RHD), because of its homology to Drosophila Runt protein, which mediates both DNA binding and heterodimerization with CBFbeta, and a carboxyl(C)-terminal region responsible for transcriptional regulation. Heterodimerization with CBFbeta enhances its DNA-binding capacity and protects it from proteolytic degradation. RUNX1 binds to the DNA consensus sequence TGTGGT and functions as a transcriptional activator or repressor, depending on promoter structure, the spliced variant expressed and the cellular context. RUNX1 is believed to act as a transcriptional organizer, recruiting other lineage-specific transcription factors to their promoters.

Expression: During embryogenesis, RUNX1 can be detected in hematopoietic stem cells and endothelial cells of the AGM region, while after organogenesis, RUNX1 is predominantly expressed in the hematopoietic system. Highest levels are found in thymus, bone marrow and peripheral blood.

*Localisation*: Nucleus.

*Function*: The RUNX1/CBFbeta transcription complex is critical for normal hematopoiesis, as revealed in RUNX1-null mice, which die during embryonic development due to failure to establish definitive hematopoiesis.
Although it is dispensable for the maintenance of adult hematopoietic stem cells, it plays an essential role in the development of the megakaryocytic and lymphoid lineages.

The role of RUNX1 in megakaryocytes is beginning to be revealed. In vitro studies suggest that RUNX1 participates in megakaryocyte lineage commitment and divergence from the erythroid pathway. While FPD/AML patients show a decrease in megakaryocyte colony growth, heterozygous or conditional biallelic deletion of RUNX1 in mice leads to increased megakaryocyte growth with a partial arrest in differentiation. Besides, several abnormalities in the lymphoid lineage have been revealed in mouse models, including defects in B- and T-cells. In contrast, despite its expression in monocytes and neutrophils and its regulation of genes specific to these cells, lack of RUNX1 has no apparent effects in monocyte or neutrophil number or function. Known targets of RUNX1 in hematopoietic cells include cytokines, cell receptors and differentiation molecules, such as GM-CSF, IL-3, myeloperoxidase, neutrophil elastase, M-CSF and TCR receptors.

**Homology:** Other members of the RUNX family include RUNX2 and RUNX3, which are alternative heterodimeric partners for CBFbeta.

**Mutations**

Note: Germline RUNX1 mutations Linkage to chromosome 21q22.12 was established in 1996 in a large FPD/AML pedigree described by Dowton and colleagues. Among genes mapping to this region, RUNX1 emerged as an attractive candidate for this disorder and subsequently, RUNX1 mutations were identified in several FPD/AML patients. Fourteen different mutations have been detected in fifteen pedigrees reported so far, including missense, nonsense and frameshift mutations and a large intragenic deletion. Most mutations are clustered in the RHD, although mutations in the C-terminal region have been found in three cases. Most frequently involved amino acids are those included in the three loops which contact the DNA-interface, comprising amino acids 74-87, 139-145 and 171-177.

In vitro functional studies have shown that RHD mutations abrogate the DNA-binding and transactivation capacity while, according to whether they retain or loose their ability to heterodimerize with CBFbeta, they interfere with the wild-type protein in a dominant-negative manner or act through haploinsufficiency, respectively.

On the other hand, C-terminal mutants have an enhanced capacity to bind DNA, due to lack of a DNA-binding inhibitory domain, and interact strongly with CBFbeta and are therefore expected to strongly repress the normal allele. Dominant-negative mutations seem to cause higher predisposition to leukemia than those acting via haploinsufficiency.

Recently, constitutional microdeletions on 21q encompassing the RUNX1 locus have been reported to cause congenital thrombocytopenia associated with mental retardation, developmental delay and predisposition to leukemia.

**Somatic:** RUNX1 is one of the genes most frequently dysregulated in leukemia, mostly through chromosomal translocations, mutations and amplifications. RUNX1 was originally cloned as the target of the t(8;21) chromosomal translocation characteristic of AML which encodes the RUNX1 (AML1) - ETO fusion product, and was subsequently found to be involved in other chromosomal translocations in both myeloid and lymphoblastic neoplasms, such as t(12;21) and t(3;21), which generate TEL - RUNX1 and RUNX1 - MDS1/EVI1 transcripts. Besides, acquired point mutations in the RUNX1 gene have been reported in 5% sporadic leukemia, predominantly in FAB subtype M0, where they are frequently biallelic. Moreover, mutations have been detected in
Schematic structure of RUNX1b protein and position of germline mutations identified in fifteen FPD/AML pedigrees. Missense mutations are show at the upper side of the panel in pale blue, while nonsense and frameshift mutations are represented in green at the bottom. A large intragenic deletion was found in one case. * indicates this mutation has been identified in two pedigrees.

approximately 8% MDS patients and in 45% secondary MDS and AML. While AML mutations occur mainly in the RHD, both N-terminal and C-terminal mutations have been reported in MDS. On the other hand, RUNX1 amplification occurs predominantly in pediatric LLA.

**References**


Ito Y. Molecular basis of tissue-specific gene expression mediated by the runt domain transcription factor PEBP2/CBF. Genes Cells. 1999 Dec;4(12):685-96


Sun L, Mao G, Rao AK. Association of CBFA2 mutation with decreased platelet PKC-theta and impaired receptor-mediated activation of GPIIb-IIa and pleckstrin phosphorylation: proteins regulated by CBFA2 play a role in GPIIb-IIIa activation. Blood. 2004 Feb 1;103(3):948-54


**This article should be referenced as such:**