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## **RUNX1 Familial Platelet Disorder with Associated Myeloid Malignancies**

Synonyms: Familial Platelet Disorder / Acute Myeloid Leukemia (FPD/AML), *RUNX1* Familial Platelet Disorder (FPD)

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## Summary

### Clinical characteristics

*RUNX1* familial platelet disorder with associated myeloid malignancies (*RUNX1*-FPDMM) is characterized by prolonged bleeding and/or easy bruising and an increased risk of developing a hematologic malignancy. *RUNX1*-FPDMM is characterized by thrombocytopenia with normal platelet size; bleeding is often greater than expected due to qualitative platelet dysfunction. Myeloid malignancies are the most common, including acute myelogenous leukemia (and myelodysplastic syndrome. T- and B-cell acute lymphoblastic leukemias and lymphomas have also been reported, as well as skin manifestations (e.g., eczema, psoriasis).

### Diagnosis/testing

The diagnosis of *RUNX1*-FPDMM is established in a proband with suggestive findings and a heterozygous germline pathogenic variant in *RUNX1* identified by molecular genetic testing.

### Management

*Treatment of manifestations:* Use of clotting promoters (e.g., desmopressin, epsilon aminocaproic acid, tranexamic acid) in instances of surgeries, injuries, or dental treatments; platelet transfusions may be used for severe bleeding or procedures with a high bleeding risk. Allogenic stem cell transplantation may be considered in individuals with early signs of malignancy and hematopoietic stem cell transplant may be used to treat myelodysplasia; however, recommendations regarding the indications and timing of stem cell transplant can vary. Emollients and topical steroids as needed for eczema; consider providing a medical letter for the school explaining easy bruising; consider use of a medical alert bracelet.

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*Surveillance:* Clinical examination for signs/symptoms of neoplasm (e.g., constitutional symptoms such as fatigue, unexplained fever, unexplained weight loss, shortness of breath) every six to 12 months. Complete blood count with differential every three to four months; bone marrow examination if constitutional symptoms and/or abnormalities on complete blood count are identified; skin exam as needed.

*Agents/circumstances to avoid:* Medications that affect platelet function (e.g., NSAIDs and antiplatelet agents), activities with a high risk of trauma (e.g., high-risk contact sports), unnecessary radiation, and smoking.

*Evaluation of relatives at risk:* It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from surveillance for malignancy and more targeted medical management.

## Genetic counseling

*RUNX1*-FPDMM is inherited in an autosomal dominant manner. Most individuals diagnosed with *RUNX1*-FPDMM inherited the causative pathogenic variant from a parent who may or may not have recognized manifestations of the disorder. If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to sibs of inheriting the pathogenic variant is 50%. If the *RUNX1* pathogenic variant identified in the proband is not detected in parental DNA, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility either of a false negative result in a parent (due to preferential loss of the chromosome with the *RUNX1* pathogenic variant), or of parental germline mosaicism. Once the *RUNX1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

## Diagnosis

### Suggestive Findings

*RUNX1* familial platelet disorder with associated myeloid malignancies (*RUNX1*-FPDMM) **should be suspected** in individuals with the following findings.

#### Clinical findings

- Abnormal bruising or bleeding (90%)
  - Bruising without known trauma
  - Excessive bleeding following surgery or trauma
  - Bleeding from the gums after brushing or flossing teeth or prolonged bleeding following dental cleaning or dental extractions
  - Obstetric and gynecologic manifestations may include menorrhagia, miscarriage, and bleeding before or after childbirth.
  - 20%-25% of individuals require platelet transfusions or medications to assist primary hemostasis such as antifibrinolytics (e.g., tranexamic acid, aminocaproic acid).
- Hematologic malignancy (up to 50%)
- Eczema (up to 50% of families)

#### Family history

- History of hematologic malignancy (50%) and/or abnormal bleeding or bruising consistent with autosomal dominant inheritance (e.g., affected males and females in multiple consecutive generations)
- Note: Absence of a known family history does not preclude the diagnosis.

#### Laboratory findings

- Mild-to-moderate thrombocytopenia ( $50\text{-}150 \times 10^9/\text{L}$ ). Platelet counts can be in the normal range in some individuals ( $>150 \times 10^9/\text{L}$ ). Severe thrombocytopenia is usually not observed except in those with acute myelogenous leukemia or myelodysplastic syndrome (MDS).
- Platelets are typically normal in size; however, individuals with both smaller and larger than normal mean platelet volume have been reported.
- Qualitative platelet defect
  - Prolonged bleeding time (not clinically performed in the current era)
  - Abnormal platelet aggregation studies are seen in most individuals with absent or decreased response to arachidonic acid and collagen. Platelets from these individuals also exhibit absent or decreased second wave response to adenosine diphosphate and epinephrine, indicating decreased platelet degranulation.
  - Platelet storage pool disorder seen on electron microscopy in about half of individuals (decrease or absence of alpha-granules or dense granules)

### Bone marrow histopathology

- Baseline morphologic abnormalities may include:
  - Hypo- or normocellular marrow for age (Marrow may become hypercellular or more hypocellular in individuals with hematologic malignancy or bone marrow failure.)
  - Atypical (but not frankly dysplastic) megakaryocytes (small in size with scant cytoplasm, and hypo-lobated nuclei with asynchronous nuclear cytoplasmic maturation)
  - Eosinophilia
- Pathologists who are not familiar with *RUNX1*-associated megakaryocytic atypia may misdiagnose megakaryocytic atypia as a dysplastic morphologic change (MDS should be considered if additional cytopenias, frank morphologic dysplasia, or expanded myeloblast populations are present).

## Establishing the Diagnosis

The diagnosis of *RUNX1*-FPDMM is **established** in a proband with suggestive findings and a heterozygous germline pathogenic variant in *RUNX1* identified by molecular genetic testing (Table 1).

Note: Identification of a heterozygous *RUNX1* variant of uncertain significance does not establish or rule out the diagnosis. Additional information on *RUNX1*-specific classification guidelines are available [Luo et al 2019].

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings may be diagnosed using gene-targeted testing (see Option 1). However, individuals with a germline *RUNX1* pathogenic variant can exhibit significant clinical heterogeneity. Individuals may present with platelet defects and/or hematologic malignancy that are indistinguishable from other inherited hematologic disorders [Luo et al 2019]. In such instances it may be more efficient to pursue genomic testing (see Option 2).

### Option 1

**Single-gene testing.** Sequence analysis of *RUNX1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. Typically, if no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

**A multigene panel** that includes *RUNX1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

## Option 2

Given that the *RUNX1* phenotype may be variable, and can be indistinguishable from many other inherited conditions, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, may be a good option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Note: (1) Testing for a germline pathogenic variant should not be performed on blood or bone marrow during active hematologic malignancy. *RUNX1* pathogenic variants are found in the cells of approximately 10% of persons with hematologic malignancy [Simon et al 2020]. (2) When clinically possible, cultured skin fibroblasts are recommended for germline testing. If this source of DNA is not available, buccal samples can be considered. However, there is a risk of peripheral blood contamination. (3) Somatic loss of heterozygosity due to uniparental disomy 21 has been identified in hematopoietic tissue of individuals with a germline *RUNX1* pathogenic variant [Glembotsky et al 2020]. This somatic change may cause a false negative molecular result when testing leukocyte or bone marrow DNA (see Molecular Pathogenesis, ***RUNX1*-specific laboratory technical considerations**).

**Table 1.** Molecular Genetic Testing Used in *RUNX1* Familial Platelet Disorder with Associated Myeloid Malignancies

Gene <sup>1</sup>	Method	Proportion of Pathogenic Variants <sup>2, 3</sup> Detectable by Method
<i>RUNX1</i>	Sequence analysis <sup>4</sup>	~80% <sup>5</sup>
	Gene-targeted deletion/duplication analysis <sup>6</sup>	~20% <sup>5</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Individuals with contiguous gene deletions of various sizes that include *RUNX1* (not included in these calculations) have been reported (see Genetically Related Disorders) [Braddock et al 2016].

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

5. Data derived from the *RUNX1* Research Program Database [Brown et al 2020]

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

## Clinical Characteristics

### Clinical Description

To date, more than 130 individuals have been identified with a germline pathogenic variant in *RUNX1* [Brown et al 2020]. The following description of the phenotypic features associated with *RUNX1* familial platelet disorder with associated myeloid malignancies (*RUNX1*-FPDMM) is based on these reports.

**Table 2.** *RUNX1* Familial Platelet Disorder with Associated Myeloid Malignancies: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Prolonged bleeding &/or easy bruising	~90%	Presentation can be variable.
Myelodysplastic syndrome / acute myeloid leukemia	~20%-50%	Brown et al [2020], Simon et al [2020]
Lymphoid malignancy	Unknown	~25% of families have at least 1 member w/lymphoid malignancy [Brown et al 2020].
Eczema	Up to 50%	Brown et al [2020]

**Prolonged bleeding.** Almost all individuals with *RUNX1*-FPDMM will experience some degree of abnormal bleeding as a consequence of their quantitative and/or qualitative platelet defect at some point. The bleeding phenotype may be highly variable, even within families. Bleeding may be subclinical in some individuals, who may not notice that their bleeding is abnormal compared to the general population or may not bring it to medical attention. Bleeding defects vary drastically in severity and may manifest as epistaxis, easy bruising, excessive bleeding during minor surgery or injuries, and/or menorrhagia. A minority of individuals require blood transfusions. Age of onset of bleeding can also be highly variable, with some individuals presenting in early infancy and others not recognizing their symptoms until much later in life.

**Predisposition to hematologic malignancies.** Individuals with *RUNX1*-FPDMM have a 25%-50% lifetime risk of developing a hematologic malignancy [Brown et al 2020]. Myeloid malignancies including acute myelogenous leukemia and myelodysplastic syndrome are the most common. T- and B-cell acute lymphoblastic leukemias and lymphomas have also been reported. The median age of onset is 33 years [Brown et al 2020, DiFilippo et al 2020].

**Eczema and other inflammatory features.** Eczema and other skin findings such as psoriasis have been reported in roughly 50% of families with *RUNX1*-FPDMM [Brown et al 2016]. Age of onset and severity of skin features is highly variable, but usually noted in childhood, mild, and managed topically.

### Genotype-Phenotype Correlations

No consistent genotype-phenotype correlations have been identified.

### Penetrance

The penetrance of germline *RUNX1* pathogenic variants is unknown. A minority of individuals have no clinical or laboratory features.

### Nomenclature

*RUNX1* was previously referred to as *AML1* and *CBFA2* [van Wijnen et al 2004].

## Prevalence

More than 130 individuals with *RUNX1*-FPDMM have been reported to date; however, it is likely that *RUNX1*-FPDMM is highly underdiagnosed [Brown et al 2020, Simon et al 2020].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with a heterozygous germline pathogenic variant in *RUNX1*.

A nonrecurrent 21q22 contiguous gene deletion syndrome that includes *RUNX1* is known to be associated with Braddock-Carey syndrome [Braddock et al 2016]. Because the breakpoints of the reported deletions of region 21q22 are variable, the resulting phenotype depends on the size of the deletion and the gene content. In general, Braddock-Carey syndrome is characterized by Pierre Robin sequence, agenesis of the corpus callosum, dysmorphic facies, developmental delay / intellectual disability, enamel hypoplasia, and congenital thrombocytopenia.

Sporadic hematopoietic neoplasms (e.g., acute myelogenous leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia), clonal cytopenias of uncertain significance [Bellissimo & Speck 2017], and sporadic solid tumors (most notably breast cancer [Chimge & Frenkel 2013]) frequently harbor somatic variants in *RUNX1* that are not present in the germline. In these circumstances predisposition to these hematopoietic neoplasms and tumors is not heritable. For more information, see Cancer and Benign Tumors.

## Differential Diagnosis

**Table 3.** Genes of Interest in the Differential Diagnosis of *RUNX1* Familial Platelet Disorder with Associated Myeloid Malignancies

Gene	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/ <i>RUNX1</i> -FPDMM	Distinguishing from <i>RUNX1</i> -FPDMM
<i>ANKRD26</i>	<a href="#">ANKRD26-related thrombocytopenia</a>	AD	Nonsyndromic thrombocytopenia w/ normal platelet size & predisposition to myeloid neoplasms	Some persons may have erythrocytosis (hemoglobin $\leq$ 18.5 g/dL) & leukocytosis.
<i>CEBPA</i>	<a href="#">CEBPA-associated familial acute myeloid leukemia</a>	AD	Familial predisposition to AML & thrombocytopenia	Leukopenia (w/ $\uparrow$ infections) & anemia
<i>DDX41</i>	<a href="#">DDX41-associated familial MDS/AML</a>	AD	Familial predisposition to MDS/AML	Some persons may have erythroid or megakaryocytic dysplasia. <sup>1</sup>
<i>ETV6</i>	<a href="#">ETV6-related thrombocytopenia</a>	AD	Nonsyndromic thrombocytopenia w/ normal platelet size & predisposition to myeloid neoplasms	Can have red cell macrocytosis & neutropenia; predisposes to lymphoid malignancy
<i>GATA2</i>	GATA2 deficiency	AD	Familial predisposition to MDS/AML	Immunodeficiency ( $\downarrow$ or absent monocytes & B- & NK-cell lymphocytes)
<i>SRP72</i>	Bone marrow failure syndrome 1 (OMIM 614675)	AD	Familial predisposition to MDS	Aplastic anemia, pancytopenia
<i>TP53</i>	<a href="#">Li-Fraumeni syndrome</a>	AD	Familial predisposition to MDS/AML	High penetrance for non-hematologic cancers (breast cancer, osteosarcoma, soft tissue sarcomas)

AD = autosomal dominant; AML = acute myeloid leukemia; DiffDx = differential diagnosis; MDS = myelodysplastic syndrome; MOI = mode of inheritance; *RUNX1*-FPDMM = *RUNX1* familial platelet disorder with associated myeloid malignancies

1. Lewinsohn et al [2016]

### Acquired disorders in the differential diagnosis of RUNX1-FPDMM

- Immune thrombocytopenia
- Secondary thrombocytopenia
- Medication-related (e.g., NSAIDs, antiplatelet agents, statins, furosemide, heparin, ranitidine, linezolid) increased risk of bruising and prolonged bleeding
- Leukemia

## Management

No clinical practice guidelines for RUNX1 familial platelet disorder with associated myeloid malignancies (RUNX1-FPDMM) have been published.

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with RUNX1-FPDMM, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 4.** Recommended Evaluations Following Initial Diagnosis in Individuals with RUNX1 Familial Platelet Disorder with Associated Myeloid Malignancies

System/Concern	Evaluation	Comment
<b>Hematologic</b>	Clinical eval by hematologist incl CBC, differential, reticulocyte count, & peripheral smear	Baseline bone marrow biopsy & aspirate may be considered.
<b>Dermatologic</b>	Clinical eval for eczema or other skin concerns as needed	
<b>Genetic counseling</b>	By genetics professionals <sup>1</sup>	To inform affected persons & their families re nature, MOI, & implications of RUNX1-FPDMM to facilitate medical & personal decision making

CBC = complete blood count; MOI = mode of inheritance; RUNX1-FPDMM = RUNX1 familial platelet disorder with associated myeloid malignancies

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse, or hematologist with expertise in these disorders

### Treatment of Manifestations

**Table 5.** Treatment of Manifestations in Individuals with RUNX1 Familial Platelet Disorder with Associated Myeloid Malignancies

Manifestation/Concern	Treatment	Considerations/Other
<b>Impaired clotting</b>	Use of clotting promoters (e.g., desmopressin, epsilon aminocaproic acid, tranexamic acid) for surgeries, injuries, or dental treatments	Platelet transfusions may be used for severe bleeding or procedures w/high bleeding risk but are not first-line therapy due to risk of alloimmunization.
<b>Myelodysplastic syndromes &amp; acute leukemias</b>	Allogenic stem cell transplantation may be considered in transplant-eligible persons w/early signs of malignancy.	<ul style="list-style-type: none"> <li>• FPDMM is not thought to be curable w/chemotherapy alone; HSCT is almost always required.</li> <li>• Test for familial RUNX1 pathogenic variant prior to using a family member as a HSCT donor. <sup>1</sup></li> </ul>
<b>Eczema</b>	Emollients & topical steroids as needed	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
<b>Family support/ resources</b>	Consider: <ul style="list-style-type: none"> <li>• Providing a medical letter for school explaining easy bruising at baseline, as referrals for social services for concern of child abuse can occur;</li> <li>• Use of a medical alert bracelet for thrombocytopenia, platelet dysfunction, or hematologic malignancy as indicated.</li> </ul>	

FPDMM = familial platelet disorder with associated myeloid malignancies; HSCT = hematopoietic stem cell transplant

1. Recurrence of leukemia was reported after a donor sib was found to have the familial *RUNX1* pathogenic variant [Owen et al 2008].

## Surveillance

Guidelines on the type of testing or frequency of surveillance have not been published.

**Table 6.** Recommended Surveillance for Individuals with *RUNX1* Familial Platelet Disorder with Associated Myeloid Malignancies

System/Concern	Evaluation	Frequency
<b>Hematologic malignancy</b>	Clinical exam for constitutional signs & symptoms of neoplasm (e.g., fatigue, unexplained fever, unexplained weight loss, shortness of breath)	Every 6-12 mos or more frequently as clinically indicated
	CBC w/differential	Every 3-4 mos
	Bone marrow exam	<ul style="list-style-type: none"> <li>• If constitutional symptoms &amp;/or abnormalities on CBC are identified</li> <li>• Consider annually (although there is no consensus on this recommendation).</li> </ul>
<b>Eczema</b>	Skin exam	As needed

CBC = complete blood count

## Agents/Circumstances to Avoid

Avoid the following:

- Medications that affect platelet function, such as NSAIDs and antiplatelet agents
- Activities with a high risk of trauma, such as high-risk contact sports

Factors such as smoking, chemical exposure, unnecessary radiation, and obesity may increase the risk of developing hematologic malignancy.

## Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from surveillance for malignancy and more targeted medical management.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

Platelet counts and bleeding complications should be monitored during pregnancy. Qualitative and quantitative platelet disorders can lead to severe bleeding before, during, or after delivery. While thrombocytopenia itself



(particularly if mild) in the absence of aggregation and storage pool disorders is unlikely to affect pregnancy, low platelet counts ( $<50 \times 10^9/L$ ) can limit the ability to receive epidural analgesia or neuraxial anesthesia. Strategies to increase platelet count (transfusion) can be considered on an individual basis in consultation with the obstetrician, hematologist, and anesthesiologist.

See [MotherToBaby](#) for further information on medication use during pregnancy.

## Therapies Under Investigation

Search [ClinicalTrials.gov](#) in the US and [EU Clinical Trials Register](#) in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

*RUNX1* familial platelet disorder with associated myeloid malignancies (*RUNX1*-FPDMM) is inherited in an autosomal dominant manner.

## Risk to Family Members

### Parents of a proband

- Most individuals diagnosed with *RUNX1*-FPDMM inherited the causative pathogenic variant from a parent, who may or may not have recognized manifestations of the disorder.
- Some individuals diagnosed with *RUNX1*-FPDMM have the disorder as the result of a *de novo* *RUNX1* pathogenic variant. The proportion of probands who have a *de novo* pathogenic variant is unknown.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to assess their genetic status and to allow reliable recurrence risk counseling. Note: Because somatically acquired loss of heterozygosity may result in a false negative molecular result when testing leukocyte DNA, use of DNA derived from non-hematopoietic tissues (e.g., skin fibroblasts, hair roots) should be considered if feasible (see Molecular Pathogenesis, ***RUNX1*-specific laboratory technical considerations**).
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband may have a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband may have inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. The frequency of *RUNX1* mosaicism is unknown. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.
  - The proband may have inherited a *RUNX1* pathogenic variant from a parent with somatically acquired loss of heterozygosity (with preferential loss of chromosomes with a pathogenic *RUNX1* variant) [Glembotsky et al 2020]. This somatic change (e.g., uniparental disomy 21) may occur in

hematopoietic tissue of individuals with a pathogenic *RUNX1* variant and may result in a decreased fraction of cells with the pathogenic variant and cause a false negative molecular result when testing leukocyte DNA (see Molecular Pathogenesis, ***RUNX1*-specific laboratory technical considerations**).

- The family history of some individuals diagnosed with *RUNX1*-FPDMM may appear to be negative because of failure to recognize the disorder in family members, due to variable expressivity (a heterozygous family member may have subclinical or normalized symptoms), early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent has the *RUNX1* pathogenic variant identified in the proband.

**Sibs of a proband.** The risk to sibs of a proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to sibs of inheriting the pathogenic variant is 50%.
  - Sibs who inherit a *RUNX1* pathogenic variant may have symptoms of easy bruising or bleeding and will have an estimated overall lifetime risk of hematologic malignancy between 20% and 50% (see Table 2).
  - Significant clinical variability is observed within families [Liew & Owen 2011].
- If the *RUNX1* pathogenic variant identified in the proband is not detected in parental DNA, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of a false negative result in a parent due to preferential loss of the chromosome with the *RUNX1* pathogenic variant and the possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *RUNX1* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for *RUNX1*-FPDMM because of the possibility that either: (1) a parent is heterozygous but does not have apparent manifestations of *RUNX1*-FPDMM because of variable expressivity or phenotypic modification resulting from somatically acquired loss of heterozygosity; or (2) a parent has germline mosaicism.

**Offspring of a proband.** Each child of an individual with *RUNX1*-FPDMM has a 50% chance of inheriting the *RUNX1* pathogenic variant.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has the *RUNX1* pathogenic variant, his or her family members may be at risk of having a *RUNX1* pathogenic variant and associated clinical manifestations including myeloid malignancy (see Clinical Description).

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *RUNX1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **RUNX1 Research Program**  
**Phone:** 805-880-4109  
**Email:** [info@runx1-fpd.org](mailto:info@runx1-fpd.org)  
[www.runx1-fpd.org](http://www.runx1-fpd.org)
- **Alex's Lemonade Stand Foundation**  
111 Presidential Boulevard  
Suite 203  
Bala Cynwyd PA 19004  
**Phone:** 866-333-1213  
[www.alexlemonade.org](http://www.alexlemonade.org)
- **Aplastic Anemia & MDS International Foundation, Inc.**  
4330 East West Highway  
Suite 230  
Bethesda MD 20814  
**Phone:** 800-747-2820  
**Email:** [help@aamds.org](mailto:help@aamds.org)  
[www.aamds.org](http://www.aamds.org)
- **National Cancer Institute (NCI)**  
**Phone:** 800-422-6237  
**Email:** [NCIinfo@nih.gov](mailto:NCIinfo@nih.gov)  
[www.cancer.gov](http://www.cancer.gov)
- **Platelet Disorder Support Association**  
**Phone:** 877-528-3538  
**Email:** [pdsa@pdsa.org](mailto:pdsa@pdsa.org)  
[www.pdsa.org](http://www.pdsa.org)

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.*

**Table A.** RUNX1 Familial Platelet Disorder with Associated Myeloid Malignancies: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<a href="#">RUNX1</a>	<a href="#">21q22.12</a>	<a href="#">Runt-related transcription factor 1</a>	<a href="#">RUNX1 database</a>	<a href="#">RUNX1</a>	<a href="#">RUNX1</a>

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for RUNX1 Familial Platelet Disorder with Associated Myeloid Malignancies ([View All in OMIM](#))

<a href="#">151385</a>	<a href="#">RUNT-RELATED TRANSCRIPTION FACTOR 1; RUNX1</a>
<a href="#">601399</a>	<a href="#">PLATELET DISORDER, FAMILIAL, WITH ASSOCIATED MYELOID MALIGNANCY; FPDMM</a>

## Molecular Pathogenesis

*RUNX1* encodes Runt-related transcription factor 1, which, along with its binding partner CBF $\beta$ , plays an important role in regulating genes associated with hematopoiesis. Known directed transcriptional targets of Runt-related transcription factor 1 include 12-lipoxygenase (ALOX12), platelet factor 4 (PF4), platelet myosin light chain (MYL9), protein kinase C- $\theta$  (PRKCC), pallidin (PLDN), RAB1B, TREML1, ITGA2, thrombopoietin receptors (MPL), PAR4 and NFE2, NOTCH4, and A4GALT [Songdej & Rao 2019].

The majority of *RUNX1* pathogenic variants occur in the Runt homology domain; however, pathogenic variants that affect splicing as well as pathogenic variants in the transactivation domain have also been reported [Luo et al 2019, Songdej & Rao 2019]. There are several reviews describing the role of somatic and germline *RUNX1* pathogenic variants [Sood et al 2017, Songdej & Rao 2019].

Malignant transformation in individuals with *RUNX1* familial platelet disorder with associated myeloid malignancies (*RUNX1*-FPDMM) is often attributable to the accumulation of additional somatic pathogenic variants in other genes (e.g., *ASXL1*, *CBL*, *CDC25C*, *FLT3*, *PHF6*, *SRSF2*, and *WT1*) and/or a loss-of-function variant in the other *RUNX1* allele [Antony-Debré et al 2016].

**Mechanism of disease causation.** *RUNX1* gene dosage is critical for thrombocyte differentiation. Functional studies have shown that *RUNX1* frameshift variants and large deletions are loss-of-function variants, leading to haploinsufficiency. Some missense and nonsense variants have been shown to act in a dominant-negative mechanism by affecting DNA binding and/or transactivation [Sood et al 2017].

***RUNX1*-specific laboratory technical considerations.** Somatically acquired loss of heterozygosity due to uniparental disomy 21 has been identified in hematopoietic tissue of individuals with a pathogenic *RUNX1* variant [Glembotsky et al 2020]. *RUNX1* is located on chromosome 21 and loss of chromosomes with a pathogenic *RUNX1* variant may occur preferentially. This somatic change results in a decreased fraction of cells with the variant and may cause a false negative molecular result when testing leukocyte or bone marrow DNA. Therefore, evaluation of genomic abnormalities with SNP array and/or evaluation of low-abundance variants with deep sequencing (>1000x read depth) should be considered in individuals clinically suspected for *RUNX1*-FPDMM who have a negative genetic test result. If feasible, using the DNA derived from non-hematopoietic tissues (e.g., skin fibroblasts, hair roots) may be considered.

## Cancer and Benign Tumors

Sporadic hematopoietic neoplasms (e.g., acute myelogenous leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia) and sporadic solid tumors (most notably, breast cancer) may occur as single tumors in the absence of any other findings of *RUNX1*-FPDMM and frequently harbor somatic variants in *RUNX1* that are not present in the germline [Chimge & Frenkel 2013, Bellissimo & Speck 2017, Brown et al 2020, Simon et al

2020]. In these circumstances, predisposition to these hematopoietic neoplasms and tumors is not heritable. A variant allele fraction of less than 40% for the *RUNX1* pathogenic variant identified in tumor tissue is suggestive of a somatic variant.

## Chapter Notes

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- 6 May 2021 (ma) Revision: added Braddock-Carey syndrome to Genetically Related Disorders
- 4 March 2021 (sw) Review posted live
- 5 October 2020 (nd) Original submission

Note: Pursuant to 17 USC Section 105 of the United States Copyright Act, the *GeneReview* "*RUNX1* Familial Platelet Disorder with Associated Myeloid Malignancies" is in the public domain in the United States of America.

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