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ANKRD26-Related Thrombocytopenia

Synonym: Thrombocytopenia 2 (THC2)

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Summary

Clinical characteristics

ANKRD26-related thrombocytopenia is characterized by lifelong mild-to-moderate thrombocytopenia with a normal platelet size and no syndromic associations. Most individuals have normal hemostasis or a mild bleeding phenotype and do not develop severe spontaneous bleeding. Some individuals may have concomitant erythrocytosis and leukocytosis. The risk for myeloid malignancies (including myelodysplastic syndrome, acute myelogenous leukemia, and chronic myelogenous leukemia) is increased in individuals with *ANKRD26* pathogenic variants.

Diagnosis/testing

The diagnosis of *ANKRD26*-related thrombocytopenia is established in a proband by the presence of lifelong thrombocytopenia and identification of a heterozygous pathogenic variant in *ANKRD26* on molecular genetic testing.

Management

Treatment of manifestations: Adjunct hemostatic agents (e.g., antifibrinolytics, desmopressin) for bleeding or a major surgical procedure; platelet transfusions are reserved for severe bleeding or procedures with a high bleeding risk.

Prevention of secondary complications: For individuals with a myeloid neoplasm, careful consideration of stem cell transplant eligibility and pre-transplant therapies undertaken through a large academic institution with experience in the management of individuals with germline predisposition syndromes.

Surveillance: Surveillance for early detection of myeloid neoplasms should include an annual complete blood count with bone marrow examination if abnormalities are noted.

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Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by evaluation of the platelet count and molecular genetic testing of the *ANKRD26* pathogenic variant in the family in order to identify as early as possible those who may benefit from surveillance.

Genetic counseling

ANKRD26-related thrombocytopenia is inherited in an autosomal dominant manner. All individuals reported to date have an affected parent. Each child of an individual with *ANKRD26*-related thrombocytopenia has a 50% chance of inheriting the *ANKRD26* pathogenic variant. Once the *ANKRD26* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible; however, phenotypic variability (due to variable expressivity) within families is observed.

Diagnosis

ANKRD26-related thrombocytopenia is a nonsyndromic congenital thrombocytopenia disorder lacking pathognomonic features and thus requiring molecular confirmation of a heterozygous *ANKRD26* pathogenic variant to establish a diagnosis. Formal diagnostic criteria have not been published.

Suggestive Findings

ANKRD26-related thrombocytopenia **should be suspected** in individuals with the following:

- Lifelong mild-to-moderate thrombocytopenia (<150 x 10^9/L, confirmed with repeat examination)
- Normal platelet size (mean platelet volume [fL] per reference interval of automated instrument)
- Absent or minimal bleeding tendency
- Family history of thrombocytopenia with an autosomal dominant pattern of inheritance
- Personal or family history of myeloid neoplasms at a young age
- Previous or suspected diagnosis of immune thrombocytopenia (ITP) without improvement on immunosuppressive treatment
- Absence of features suggesting syndromic association

Establishing the Diagnosis

The diagnosis of *ANKRD26*-related thrombocytopenia **is established** in a proband by the presence of lifelong thrombocytopenia and identification of a heterozygous pathogenic variant in *ANKRD26* on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ANKRD26* should include the 5' untranslated region (5'UTR) to detect known regulatory pathogenic variants. Of note, all individuals diagnosed with *ANKRD26*-related thrombocytopenia to date have had pathogenic variants identified by *ANKRD26* sequence analysis, primarily of the 5'UTR; therefore, the utility of *ANKRD26* deletion/duplication analysis is unclear.
- **A multigene panel** that includes *ANKRD26* and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included and the sensitivity of multigene panels 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of unknown significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include custom laboratory-designed panels and/or

custom phenotype-focused exome analysis. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests (5) The multigene panel should include sequence analysis of *ANKRD26* 5'UTR.

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

Table 1. Molecular Genetic Testing Used in *ANKRD26*-Related Thrombocytopenia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ANKRD26	Sequence analysis [3, 4]	42 of 42 reported probands [5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. 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.
4. Must include sequencing of 5'UTR, which has a significant number of the known pathogenic variants
5. Al Daama et al [2013], Noris et al [2013], Marquez et al [2014], Ouchi-Uchiyama et al [2015], Perez Botero et al [2015], Averina et al [2017], Ferrari et al [2017], Marconi et al [2017]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Individuals with *ANKRD26*-related thrombocytopenia usually present with lifelong mild-to-moderate thrombocytopenia with a normal platelet size and no syndromic associations. Incidental presentation following routine complete blood count is not uncommon. Some individuals are identified after developing a myeloid neoplasm such as acute myeloid leukemia or myelodysplastic syndrome.

Bleeding history. Most individuals have normal hemostasis or a mild bleeding phenotype and do not develop severe spontaneous bleeding.

Complete blood counts

- Mild to moderate thrombocytopenia (50 to 150 x 10^9/L) is usually observed. Some individuals can have platelets as low as <10 x 10^9/L while others have transient correction of thrombocytopenia to >150 x10^9/L during infectious episodes.
- Platelet size is normal by automated method (mean platelet volume) or microscopic analysis.
- Platelets have normal granularity on light microscopy.
- Individuals can have erythrocytosis, with some presenting with hemoglobin as high as 18.5 g/dL.
- Some individuals have presented with leukocytosis.

Platelet structure and function studies. While abnormal platelet aggregation studies, decreased expression of platelet glycoprotein Ia (GPIa), decreased alpha granules, and increased canalicular network on platelet transmission electron microscopy have been reported, no consistent or definitive structural or functional alterations have been established.

Bone marrow biopsy. On bone marrow biopsy, megakaryocytes are increased in number but small and hypolobated [Noris et al 2011, Perez Botero et al 2015].

Predisposition to myeloid malignancies. The incidence of myeloid malignancies, including myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML), and chronic myelogenous leukemia, is increased in families with pathogenic variants in *ANKRD26*, with one series showing an estimated 24-fold increased risk of AML compared to the general population [Noris et al 2013]. Prevalence of AML or MDS among individuals with *ANKRD26*-related thrombocytopenia is about 8% (see Molecular Genetics, **Cancer predisposition)**.

Genotype-Phenotype Correlations

No consistent genotype-phenotype correlations are known.

Penetrance

Penetrance for thrombocytopenia is complete in individuals with an *ANKRD26* pathogenic variant. The risk of transformation to a myeloid malignancy is variable [Noris et al 2013].

Prevalence

The prevalence for this rare disorder is unknown. Fewer than 200 affected individuals have been reported. However, in one large cohort, *ANKRD26* 5'UTR pathogenic variants appeared to be one of the most frequent causes of inherited thrombocytopenia [Noris et al 2011]. Due to the recent description of this entity and difficulties in diagnosis, the number of affected individuals may be higher.

Genetically Related (Allelic) Disorders

Recent evidence suggests that germline heterozygous pathogenic variants leading to N-terminal truncated ANKRD26 isoforms may predispose to myeloid neoplasms by the same gain-of-function mechanisms as pathogenic variants in the 5'UTR region. Interestingly, these individuals may present without thrombocytopenia [Marconi et al 2017].

Differential Diagnosis

Due to the clinical and genetic heterogeneity and low incidence of inherited platelet disorders, the diagnosis is challenging, and sometimes inherited platelet disorders are misdiagnosed as idiopathic thrombocytopenic purpura (immune thrombocytopenia; ITP). Complex diagnostic algorithms have been proposed [Balduini et al 2013a].

Table 2. Disorders to Consider in the Differential Diagnosis of *ANKRD26*-Related Thrombocytopenia

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
Familial platelet disorder / acute myeloid leukemia (FPD/AML)	*RUNX1*	AD	Nonsyndromic thrombocytopenia w/normal platelet size & predisposition to myeloid neoplasms	FPD/AML: • Can have normal platelet counts • More bleeding due to platelet storage pool disorder (dense granule deficiency)

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
ETV6-related thrombocytopenia (thrombocytopenia-5, *ETV6*-RT)	*ETV6*	AD	Nonsyndromic thrombocytopenia w/normal platelet size & predisposition to myeloid neoplasms	*ETV6*-RT: • Can have red cell macrocytosis & neutropenia • Predisposes to lymphoid malignancy
CYCS-related thrombocytopenia (thrombocytopenia-4, *CYCS*-RT; OMIM 616216)	*CYCS*	AD	Nonsyndromic thrombocytopenia w/normal platelet size	*CYCS*-RT: Does not predispose to neoplasms
Immune thrombocytopenia (ITP)	NA	NA	Thrombocytopenia w/normal (or mildly elevated) platelet size, minimal bleeding unless thrombocytopenia is severe	ITP: • Sporadic • Family history negative • Prior platelet count normal • Responds to immunosuppressive treatments • Does not predispose to malignancy

AD = autosomal dominant; MOI = mode of inheritance; NA = not applicable; RT = related thrombocytopenia

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ANKRD26*-related thrombocytopenia, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Clinical evaluation by a hematologist and a complete blood count including peripheral smear review for early detection of myeloid neoplasms
- Consideration of bone marrow aspirate and biopsy at initial evaluation to exclude hematologic malignancies if there are other cytopenias, or abnormalities in:
  - Mean corpuscular volume
  - Cell morphology
  - Leukocyte differential
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Most individuals are asymptomatic and undergo observation and surveillance.

When bleeding is present or a major surgical procedure is required, adjunct hemostatic agents such as antifibrinolytics or desmopressin can be given. Platelet transfusions are reserved for severe bleeding or procedures with a high bleeding risk [Balduini et al 2013b].

Thrombopoietin analogs have been used selectively for short periods of time (preoperative). The long-term safety has not been established [Pecci 2013, Fiore et al 2016].

Prevention of Secondary Complications

Once a myeloid neoplasm has been diagnosed, careful consideration of stem cell transplant eligibility and pre-transplant therapies should be undertaken. This is best accomplished at a large academic institution with experience in the management of individuals with germline predisposition syndromes [Babushok et al 2016].

Surveillance

Surveillance for early detection of myeloid neoplasms is indicated in all individuals with *ANKRD26*-related thrombocytopenia. Guidelines have not been published on the type of testing or frequency of surveillance. A complete blood count on an annual basis with bone marrow examination if abnormalities are noted is commonly recommended.

Agents/Circumstances to Avoid

If a myeloid neoplasm that requires allogeneic stem cell transplantation develops and a related donor is being considered, a donor who does not have the *ANKRD26* pathogenic variant present in the family should be used [Godley 2014].

Evaluation of Relatives at Risk

It is appropriate to consider clarifying the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by evaluation of the platelet count and molecular genetic testing of the *ANKRD26* pathogenic variant in the family in order to identify those who may benefit from surveillance.

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. While the thrombocytopenia itself (particularly if mild) is unlikely to affect the pregnancy, low platelet counts can limit the ability to receive epidural analgesia or neuroaxial anesthesia. Strategies to increase platelet count (transfusion) can be considered on an individual basis in consultation with the anesthesiologist.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

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

ANKRD26-related thrombocytopenia is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- To date, all individuals diagnosed with *ANKRD26*-related thrombocytopenia have an affected parent, either identified by molecular testing or suspected based on pedigree analysis or reported history of thrombocytopenia. The degree of thrombocytopenia varies between and within families, and transient increase in platelet counts during inflammatory events may occur, making molecular genetic testing more accurate than assessment of thrombocytopenia for diagnosis of affected relatives [Noris et al 2011].
- Some individuals diagnosed with *ANKRD26*-related thrombocytopenia could have the disorder as the result of a *de novo ANKRD26* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is unknown.
- Molecular genetic testing is recommended for the parents of a proband with a pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- The family history of some individuals diagnosed with *ANKRD26*-related thrombocytopenia may appear to be negative because of failure to recognize the disorder in family members with very mild thrombocytopenia or transient elevation of platelet counts, or early death of the parent before the onset of symptoms. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

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

- If a parent of the proband is affected, the risk to the sibs is 50%. Although penetrance of thrombocytopenia is complete, intrafamilial variability in the degree of thrombocytopenia and transient increase in platelet counts during inflammatory events may occur, making molecular genetic testing more accurate than assessment of thrombocytopenia for diagnosis of affected relatives.
- If the parents of the proband have been tested for the *ANKRD26* pathogenic variant identified in the proband and a parent has the variant, the risk to the sibs of inheriting the variant is 50%. Penetrance for the thrombocytopenia phenotype is complete with variable severity.
- If the *ANKRD26* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the empiric recurrence risk to sibs is estimated at 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *ANKRD26* pathogenic variant but are clinically unaffected with normal platelet counts on multiple occasions, the risk to the sibs of a proband appears to be low. The sibs of a proband with reportedly unaffected parents in whom confirmatory platelet counts are not available are still at increased risk for *ANKRD26*-related thrombocytopenia because of the possibility of unrecognized diagnosis in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *ANKRD26*-related thrombocytopenia has a 50% chance of inheriting the *ANKRD26* pathogenic variant. Molecular genetic testing is recommended for the offspring of a proband with a pathogenic variant as intrafamilial variability in the degree of thrombocytopenia and transient increase in platelet counts during inflammatory events may obscure diagnosis.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *ANKRD26* pathogenic variant, his or her family members may be at risk.

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.

Predictive testing for at-risk apparently asymptomatic adult family members requires prior identification of the *ANKRD26* pathogenic variant in the family.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ANKRD26* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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.

- **MedlinePlus**
  Thrombocytopenia
- **Platelet Disorder Support Association**
  Phone: 877-528-3538
  Email: pdsa@pdsa.org
  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. ANKRD26-Related Thrombocytopenia: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ANKRD26	10p12.1	Ankyrin repeat domain-containing protein 26	ANKRD26	ANKRD26

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 ANKRD26-Related Thrombocytopenia (View All in OMIM)

188000	THROMBOCYTOPENIA 2; THC2
610855	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 26; ANKRD26

Molecular Pathogenesis

Gene structure. *ANKRD26* contains 34 exons, and the longest transcript variant is NM_014915.2 (NC_000010.11). *ANKRD26* is thought to be an ancestral member of the POTE gene family [Lee et al 2006]. Alternative transcripts and multiple splice isoforms have been identified. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The great majority of reported pathogenic variants are single-nucleotide substitutions and small deletions located in a 22-nucleotide region within the 5'UTR that contains transcription factor binding sites. A recent report with in vivo and in vitro functional studies suggests the presence of truncating variants outside of the 5'UTR that may lead to predisposition to a myeloid disorder without thrombocytopenia [Marconi et al 2017].

Normal gene product. NM_014915.2 encodes the 1,710-amino-acid protein NP_055730.2. ANKRD26 is a 192-kd protein that contains N-terminal ankyrin repeat domains and C-terminal spectrin helices, which may serve to mediate protein-protein interactions, including with the cytoskeleton. ANKRD26 is expressed in the brain, gastrointestinal tract, liver, adipose, hematopoietic, and reproductive tissues; however, the exact cellular function of ANKRD26 is unknown.

Abnormal gene product. Pathogenic variants in the 5'UTR of *ANKRD26* have been shown to disrupt binding of runt-related transcription factor 1 (RUNX1) and friend leukemia integration 1 (FLI1) transcription factors. During normal megakaryopoiesis, RUNX1 and FLI1 downregulate expression of ANKRD26. Loss of RUNX1 and FLI1 transcription factor binding leads to overexpression of the ANKRD26 protein in megakaryocytes and defective pro-platelet formation. Accumulation of ANKRD26 in megakaryocytes also increases signaling through the TPO/MPL and MAPK/ERK pathways, which could explain the increased risk of myeloid transformation. Further studies are needed to validate this theory [Bluteau et al 2014].

Cancer predisposition. The molecular basis for the predisposition to myeloid malignancies in individuals with *ANKRD26*-related thrombocytopenia is unknown. The predisposition is suspected to be related to thrombopoietin hypersensitivity leading to increased proliferation in the context of increased ANKRD26 expression [Balduini et al 2018]. Acquisition of somatic pathogenic variants in epigenetic regulators, transcription factors, and cell cycle regulators has been described at the time of myeloid clonal evolution in individuals with different types of syndromes with germline predisposition to malignancy and is linked to the transformation event [Perez Botero et al 2018].

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Chapter Notes

Author Notes

Juliana Perez Botero, Stefanie N Dugan, and Matthew W Anderson are part of a multidisciplinary clinical laboratory genetics team that analyzes and interprets results of molecular testing of patients with non-malignant hematologic disorders in the context of the clinical phenotype. From a research standpoint, they focus on generating data to increase the robustness of the phenotype-genotype correlation for specific non-malignant hematologic disorders and generate algorithms for time- and cost-effective molecular diagnosis.

Website: www.versiti.org

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