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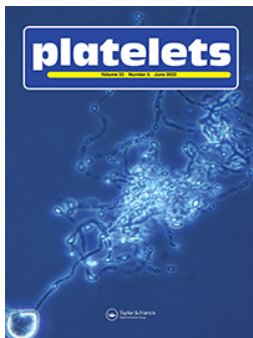
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Prevalence and natural history of variants in the *ANKRD26* gene: a short review and update of reported cases

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Abstract

ANKRD26 is a highly conserved gene located on chromosome 10p12.1 which has shown to play a role in normal megakaryocyte differentiation. *ANKRD26*-related thrombocytopenia, or thrombocytopenia 2, is an inherited thrombocytopenia with mild bleeding diathesis resulting from point mutations in the 5'UTR of the *ANKRD26* gene. Point mutations in the 5'UTR region have been shown to prevent transcription factor-mediated downregulation of *ANKRD26* in normal megakaryocyte differentiation. Patients with *ANKRD26*-related thrombocytopenia have a predisposition to developing hematological malignancies, with acute myeloid leukemia and myelodysplastic syndrome most commonly described in the literature. We review the clinical features and biological mechanisms of *ANKRD26*-related thrombocytopenia and summarize known cases in the literature.

Keywords

ANKRD26, inherited thrombocytopenia AML, MDS, platelet disorder, thrombocytopenia

History

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Introduction

Inherited thrombocytopenias (IT) are a group of disorders which present with a reduced platelet count but varied functional and morphological platelet characteristics. Some ITs are associated with extra-hematological manifestations such as sensorineural deafness (*MYH9*-related disease, *DIAPH1*-related disease) or myopathy (Storkmorken syndrome) whilst others have a predisposition to hematological malignancies such as acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and myelodysplastic syndrome (MDS) [1–4]. At least 40 genes and their mutations have been implicated in the development of inherited thrombocytopenia [3,5,6]. Definitive identification of the genetic nature of thrombocytopenia can be important as some forms differ in disease history and prognosis. Molecular diagnosis may impact clinical management, including monitoring for associated hematological malignancies.

ANKRD26-related thrombocytopenia (*ANKRD26*-RT), also known as thrombocytopenia 2 (THC2) (OMIM #188000), is a non-syndromic autosomal dominant thrombocytopenic disorder [7]. Though first described in a large Italian family, in which 17 individuals were affected and the gene locus on chromosome 10

identified using linkage analysis and candidate mutation screening, localization of pathological variants to the 5' untranslated region (5'UTR) of *ANKRD26* was not made until 2011 [8,9]. Since then, multiple causative variants have been shown to be the result of single nucleotide changes in the highly conserved 5' UTR region of the gene [10,11]. Case reports of variants in the coding region segregating with thrombocytopenia have also been reported [12–14].

Clinical features

Patients with *ANKRD26*-RT typically have lifelong mild ($100\text{--}150 \times 10^9$ cells/L) to moderate ($50\text{--}99 \times 10^9$ cells/L) thrombocytopenia, although counts may temporarily normalize in response to infection or inflammation [5,15]. The bleeding phenotype is variable. Most have a normal or mild bleeding phenotype without a history of spontaneous or prolonged surgical bleeding [7,16]. However, some individuals experiencing spontaneous epistaxis, bruising, or menorrhagia have also been reported. Morphologically, platelets appear normal in size and mean platelet volume is usually within normal range. Under light microscopy, platelets appear predominantly normogranular, with occasional hypogranular forms noted in some individuals. By electron microscopy, a reduction in alpha-granules has been described, as well as, increased particulate proteasome-rich cytoplasmic structures, the cause of which is yet to be clarified [16,17]. Platelet aggregation studies are often normal, however, reduced platelet responses to arachidonic acid and epinephrine have been reported. GPIa is commonly reduced when evaluated by flow cytometry and up to a sevenfold increase in serum thrombopoietin levels is seen in some cases [10,11,16]. Dysmegakaryopoiesis with an increase in small and hypolobulated megakaryocytes with reduced cytoplasmic volume is commonly cited in those who have undergone bone marrow biopsies [11,18]. Hemoglobin and white cell counts are generally within

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the normal range, with inconsistent reports of leukocytosis and erythrocytosis described [10,19].

Predisposition to malignancy

A clinically important feature of *ANKRD26*-RT reported in the literature is the increased risk of developing hematological malignancy. AML and MDS are the most commonly described, though there are some reports of lymphoid malignancies and a single case report of a patient with a 5'UTR mutation developing multiple myeloma [6,10–12,16,20]. An extended case series of 118 subjects with confirmed or highly probable *ANKRD26*-RT revealed an 8% incidence of myeloid malignancy (AML, MDS, and chronic myeloid leukemia (CML)) [10]. An estimated 24-fold increase in acute leukemia incidence alone is reported compared to the general population in this study, and there have been multiple other case reports describing affected patients or their relatives developing hematological malignancy (Table I).

Differential diagnosis

Diagnosis of *ANKRD26*-RT may be difficult due to the lack of distinct clinical and laboratory characteristics [16]. In many cases, patients may be misdiagnosed with immune thrombocytopenia (ITP), which should be a diagnosis of exclusion. This is especially the case if there is no obvious family history of thrombocytopenia or if the patient has had fluctuating platelet counts in the past [28,29]. There are also documented cases of patients being incorrectly diagnosed with MDS on the basis of persistently low platelet counts and bone marrow biopsy demonstrating

dysmegakaryopoiesis, both of which may be features of *ANKRD26*-RT [30].

Other ITs to consider which may also present with thrombocytopenia with normal platelet size include *RUNX1*-related thrombocytopenia (*RUNX1*-RT), *ETV6*-related thrombocytopenia (*ETV6*-RT) and *CYCS*-related thrombocytopenia (*CYCS*-RT) [3]. Of these, *RUNX1*-RT demonstrates a 30–40% lifetime risk of developing MDS/AML and *ETV6*-RT conferring a 20% lifetime risk of B-ALL with a 30% overall lifetime risk of hematological malignancy [1,5,31–33].

Pathophysiology

Regulation of *ANKRD26* expression

ANKRD26 is located on chromosome 10p12.1 and contains 34 exons that result in a number of protein isoforms expressed at low levels in multiple human tissues, including platelets, leukocytes, adrenal glands, prostate, ovary, liver, spleen, and central nervous system [34,35]. *ANKRD26* shares regions of homology with the POTE family of genes that are characterized by ankyrin repeats (involved in protein–protein interactions) close to the N-terminal region and a helical region that forms coiled-coil domains similar to that of spectrins, suggesting involvement in signal transmission across the plasma membrane (Figure 1b) [36–38]. *ANKRD26* is highly conserved between the different species, suggesting an important function [38,39]. Mouse Ankrd26 protein localizes to the cell membrane in cell lines and human *ANKRD26* protein is identified in centriolar distal appendages and cilial basal bodies in human cell lines [39–41].

Table I. Malignancies associated with variants in the 5'UTR sequence of *ANKRD26*.

Reference	Individual families by mutation	Number of affected patients in described families with a confirmed diagnosis of <i>ANKRD26</i> -RT with personal or family history of malignancy	Described malignancy developing in a participant with confirmed <i>ANKRD26</i> -RT	Malignancy described in a 1 st degree relative of the screened participant with <i>ANKRD26</i> -RT where the affected relative was unavailable to provide samples to confirm a diagnosis of <i>ANKRD26</i> -RT
[11], [21]	c.-118 C > A	N/A	-	Leukemia (undefined)
	c.-125 T > G	7	Acute Leukemia (5 x myeloid, 2x undefined)	-
	c.-125 T > G			-
	c.-127 A > T			Leukemia (undefined)
	c.-127 A > T			-
	c.-134 G > A			-
	c.-128 G > A	2	CML, MDS and CLL (MDS and CLL diagnosed in same patient)	-
	c.-127 A > T	1	CLL	-
[12]	c.-125 T > G	1	AML	-
[19]	c.-128 G > A	6	2 x AML	-
	c.-127 A > T	5	1x AML	-
	c.-127 A > T	4	MDS	-
	c.-134 G > C	4	CML	-
[20]	c.-128 G > A	1	Multiple myeloma	-
[22]	c.-127 A > T	1	CML	N/A
[23]	c.-116 C > T	1	CMML	-
[24]	c.-140 C > G	1	-	Prostate Ca
	c.-140 C > G	1	Renal Ca	-
	c.-128 G > A	1	-	AML
	c.-140 C > G	1	Breast Ca	-
	c.-140 C > G	1	AML	-
	c.-118 C > T	2	MDS/AML (2 individuals with MDS/AML)	1 additional relatives with MDS/AML
[26]	c.-118 C > T	1	-	Leukemia (undefined)
[27]	c.-118 C > T	1	-	Leukemia (undefined)

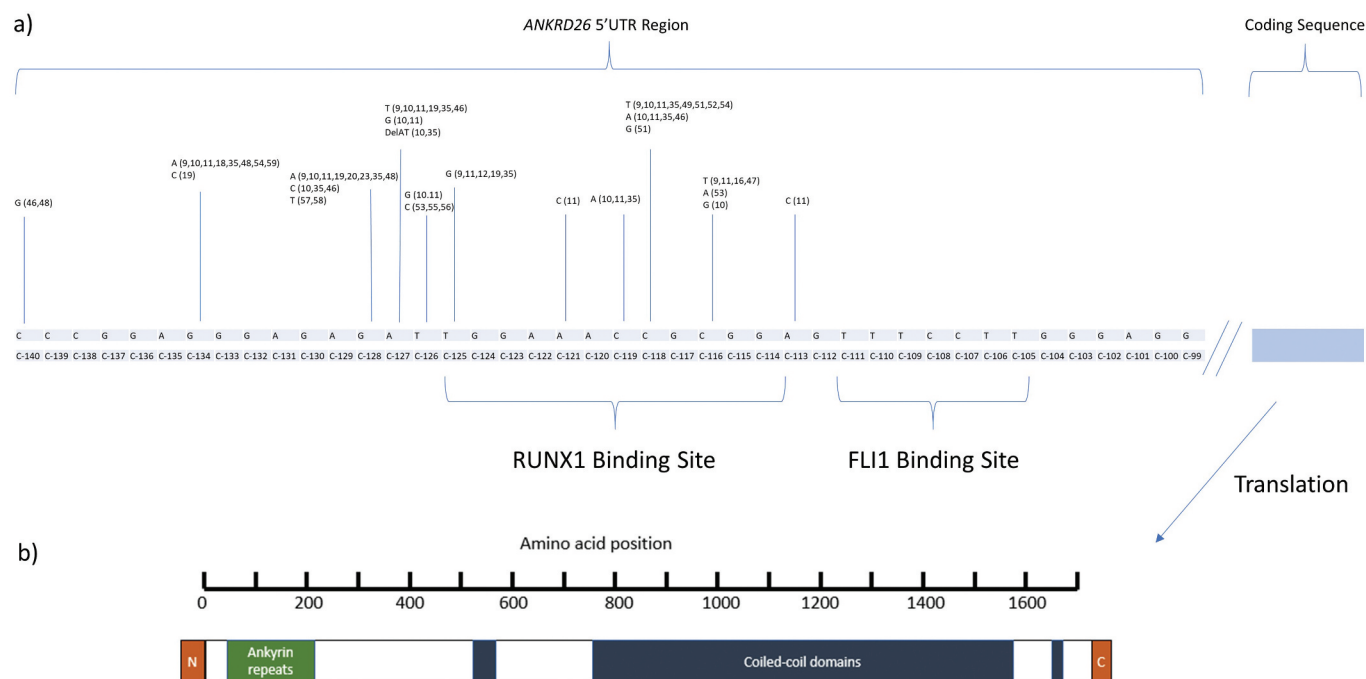


Figure 1. (a) Schematic structure of 5'UTR of *ANKRD26* mapping single point variants currently identified in the literature. (b) General structure of *ANKRD26* protein [36].

In healthy subjects, *ANKRD26* mRNA expression is high in CD34+ progenitor cells and immature megakaryocytes, and decreases over time, becoming almost undetectable in mature platelets [42]. Predictive software identified two transcription factors that bind the *ANKRD26* 5' UTR: runt-related transcription factor 1 (RUNX1) and friend leukemia integration 1 (FLI1). Knockdown of either gene in human megakaryocytes led to increased *ANKRD26* mRNA expression, while overexpression of these genes in K562 cell lines led to decreased *ANKRD26* mRNA. The effect was synergistic when both genes were overexpressed. Other studies suggest metabolic and/or inflammatory factors may also influence mRNA expression in mouse adipose tissue and human leukocytes through epigenetic alterations [43,44]. Taken together, these lines of evidence suggest expression of *ANKRD26* is regulated by interaction of transcription factors with the 5'UTR and epigenetic alterations.

Mechanisms contributing to thrombocytopenia

The 5'UTR regulatory sequence of *ANKRD26* is the most common site of single nucleotide variants identified in *ANKRD26*-RT. A total of 318 patients reported in the literature have a single point variant in this region (Table II). The most common variants include c.-128 G > A, c.-134 G > A and c.-127A>T, and lie close to RUNX1 and FLI1 binding sites (Figure 1a). These single nucleotide variants in the 5' UTR alter *ANKRD26* transcription by preventing RUNX1/FLI1-mediated repression and result in persistently high levels of *ANKRD26* mRNA at all stages of platelet development [42,52]. Electron microscopy of megakaryocyte cell lines from these patients showed slightly lower ploidy, decreased granule concentration, and abnormal proplatelet formation compared to controls.

Components of the mitogen-activated protein kinase (MAPK) pathways appear to play an important role in this process, because the megakaryocytic changes were associated with increased ERK phosphorylation, and were abrogated by *ANKRD26* knockdown or ERK pathway inhibition using a MEK inhibitor [42]. MEK (also

known as MKK or MAP2K) inhibition has previously been shown to increase ploidy and proplatelet formation in thrombopoietin-stimulated human megakaryocytes [53]. Therefore, the evidence suggests that persistence of *ANKRD26* expression in *ANKRD26*-RT leads to persistent ERK activation, which may in turn be responsible for, or contribute to, reduced megakaryocyte ploidy, impaired proplatelet formation, and subsequent thrombocytopenia.

At least one other mechanism for increased *ANKRD26* expression has been described in a thrombocytopenic family using long-read genomic sequencing. In this pedigree, a complex structural variant resulting in a paired duplication-inversion of part of the *ANKRD26* gene was identified that caused a juxtaposition of the promoter of *WAC* and exons 10–34 of *ANKRD26*. This gene duplication resulted in high *WAC*-*ANKRD26* mRNA levels and increased ERK phosphorylation similar to the phenotype caused by 5'UTR variants [54].

To date, no animal model of *ANKRD26*-RT has been described. A mouse *Ankrd26* knockdown model did not report blood abnormalities but showed mice with hyperphagia, organomegaly, obesity, and reduced expression of ciliary proteins in the brain [40,43,55].

ANKRD26 function in other cellular processes - the centrosome

As suggested by its localization, *ANKRD26* appears to play a role in centriole biology [41]. Centrioles are important in ciliogenesis and motility. They are components of centrosomes that have been implicated in cancer pathogenesis [56,57]. Centrosome amplification triggers p53-dependent apoptosis through activation of a multiprotein complex known as the PIDDosome [56]. In centrosome amplification (e.g. cytokinesis failure), *ANKRD26* recruits the p53-induced death domain protein 1 (PIDD1) to the centriole distal appendages to form part of the PIDDosome [57–59]. When *ANKRD26* is inactivated, cells cannot sustain PIDDosome assembly and show enhanced growth following centrosome amplification [57,59]. Whether these actions of

Table II. A summary of point mutations in the 5' untranslated region of the *ANKRD26* gene as reported in the literature. Mean averages reported where data available and ranges and number of individuals accounted for are in brackets.

5' UTR mutation	Number of families	Number of patients	Mean platelet count (x10 ⁹ /L)	Mean MPV (fl)	Mean Hb (g/L)	Mean WBC (x10 ⁹ /L)	Mean TPO (pg/mL)	Reference
c.-113A>C	1	3	85 (23–176) (n = 3)	11.43 (11–12.1) (n = 3)	12.53 (11.9–13.2) (n = 3)	3.9 (2.71–5.6) (n = 3)	-	[11]
c.-116C>A	1	1	82 (n = 1)	9.3 (n = 1)	13.5 (n = 1)	11.9 (n = 1)	-	[45]
c.-116C>G	1	3	70.6 (45–107) (n = 3)	9.55 (9.4–9.7) (n = 3)	12.85 (12.1–13.6) (n = 3)	11.7 (10.6–12.8) (n = 3)	-	[10]
c.-116C>T	3	10	52.14 (36–74) (n = 7)	10.85 (10.5–11.2) (n = 2)	14.95 (13.9–16) (n = 2)	11.04 (6.08–16) (n = 2)	-	[9,11,16,23]
c.-118C>A	4	10	58.2 (15–100) (n = 10)	9.59 (8.68–10.5) (n = 10)	15.08 (12.3–16.3) (n = 10)	9 (6.8–12.6) (n = 6)	206 (132–280) (n = 2)	[10,11,22,42]
c.-118C>T	10	16	47.69 (7–73) (n = 13)	9.84 (7.7–11.6) (n = 12)	13.1 (10.4–15.3) (n = 10)	9.88 (5.61–17.5) (n = 7)	258.3 (39–497) (n = 4)	[9–11,25–27,42,46]
c.-118C>G	1	1	43 (n = 1)	11 (n = 1)	-	-	-	[26]
c.-119C>A	3	5	50.96 (36–81) (n = 5)	9.3 (6.2–11.3) (n = 5)	13.5 (12.2–14.2) (n = 5)	7 (4.7–9.6) (n = 4)	-	[10,11,42]
c.-121A>C	1	3	63 (28–87) (n = 3)	10.26 (10–10.8) (n = 3)	15.6 (12.8–17) (n = 3)	15.45 (11.6–21.33) (n = 3)	-	[11]
c.-125 T > G	6	12	28.25 (7–12) (n = 4)	7.98 (6.5–10.8) (n = 4)	15.45 (12–17.3) (n = 4)	10.45 (7–13.8) (n = 4)	190.2 (148.4–232) (n = 2)	[9,11,12,19,42]
c.-126 T > C	3	3	22.3 (19–27) (n = 3)	12.2 (n = 1)	14.35 (13.8–14.9) (n = 2)	5.5 (n = 1)	-	[45,47,48]
c.-126 T > G	2	4	36.74 (14–80) (n = 4)	9.98 (8.1–10.9) (n = 4)	15.67 (13.7–16.5) (n = 4)	8.88 (7.3–12.19) (n = 4)	-	[10,11]
c.-127A>G	3	13	93.29 (46–147) (n = 13)	8.39 (6.48–9.5) (n = 13)	15.3 (12.4–18.3) (n = 11)	8.69 (6.1–11.7) (n = 13)	-	[10,11]
c.-127A>T	14	54	44.78 (10–94) (n = 34)	9.98 (7.1–14.3) (n = 30)	14.12 (10.5–17.2) (n = 31)	8.71 (5.3–12.1) (n = 23)	165.5 (106–190) (n = 8)	[9–11,19,22,42]
c.-127delAT	2	10	51.86 (26–96) (n = 10)	10.21 (8.7–11) (n = 10)	14.28 (10.4–16.6) (n = 10)	7.96 (5.8–13.4) (n = 10)	140.25 (97–178) (n = 4)	[10,42]
c.-128 G > A	24	76	32.4 (5–75) (n = 51)	8.77 (6.3–11.6) (n = 31)	14.58 (10.2–18.4) (n = 49)	9.18 (5.1–21) (n = 44)	136.67 (104–191) (n = 3)	[9–11,19,20,24,30,42]
c.-128 G > C	2	4	38.75 (24–81) (n = 4)	9.95 (7.9–14) (n = 4)	13.48 (12–14.9) (n = 4)	9.35 (6.6–12.1) (n = 2)	185 (n = 1)	[10,22,42]
c.-128 G > T	2	13	36.92 (19–70) (n = 13)	9.73 (7.9–12.5) (n = 7)	12 (6.9–14.9) (n = 13)	9.64 (4.98–14.4) (n = 7)	163 (49.76–288.58) (n = 7)	[49,50]
c.-134 G > A	15	59	44.89 (7–106) (n = 45)	8.69 (5.7–11.1) (n = 44)	14.76 (10.5–17.8) (n = 43)	9.34 (5.10–16.4) (n = 31)	-	[9–11,18,24,42,46,51]
c.-134 G > C	2	7	-	-	-	-	-	[19]
c.-134 G > A and c.-140C>G	1	1	70 (n = 1)	9 (n = 1)	12 (n = 1)	-	-	[24]
c.-140C>G	6	9	91.78 (50–200) (n = 9)	9.56 (8–11.7) (n = 9)	12.73 (9.5–14.1) (n = 9)	-	-	[22,24]
Totals:	107	317						

ANKRD26 protein play any role in the pathogenesis of ANKRD26-RT is unknown.

Concluding remarks

ANKRD26-RT is characterized by a relatively nonspecific phenotype of mild to moderate thrombocytopenia with normal platelet size and function. Most individuals lack significant mucocutaneous bleeding symptoms. A concerning association with hematological malignancy has been observed in cohorts with variants in the 5'UTR region. However, precise prevalence estimates and strategies to guide clinical monitoring, counseling, and treatment will only be possible through further analysis of large patient cohorts and exploration of the pathophysiological mechanisms underpinning this disorder.

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References

- Paola JD, Porter CC. ETV6-related thrombocytopenia and leukemia predisposition. *Blood* 2019;134(8):663–667. doi:10.1182/blood.2019852418.
- Morgan NV, Daly ME. Gene of the issue: RUNX1 mutations and inherited bleeding. *Platelets* 2017;28(2):1–3. doi:10.1080/09537104.2017.1280151.
- Almazni I, Stapley R, Morgan NV. Inherited thrombocytopenia: update on genes and genetic variants which may be associated with bleeding. *Front Cardiovasc Med* 2019;6:80. doi:10.3389/fcvm.2019.00080.
- Palma-Barqueros V, Revilla N, Sánchez A, Cánovas AZ, Rodríguez-Alén A, Marín-Quílez A, González-Porras JR, Vicente V, Lozano ML, Bastida JM, et al., Inherited platelet disorders: an updated overview. *Int J Mol Sci* 2021;22(9):4521. doi:10.3390/ijms22094521.
- Galera P, Dulau-Florea A, Calvo KR. Inherited thrombocytopenia and platelet disorders with germline predisposition to myeloid neoplasia. *Int J Lab Hematol* 2019;41(S1):131–141. doi:10.1111/ijlh.12999.
- Martin ES, Ferrer A, Mangaonkar AA, Khan SP, Kohorst MA, Joshi AY, Hogan WJ, Olteanu H, Moyer AM, Al-Kali A, et al., Spectrum of hematological malignancies, clonal evolution and outcomes in 144 Mayo Clinic patients with germline predisposition syndromes. *Am J Hematol* 2021;96(11):1450–1460. doi:10.1002/ajh.26321.
- Botero JP, Dugan SN, Anderson MW. ANKRD26-related thrombocytopenia. In: Adam MP, Ardinger HH, Pagon RA, editors. *GeneReviews®*. Seattle:University of Washington, Seattle; 2018 Jun 21. p. 1993–2022
- Savoia A, Vecchio MD, Totaro A, Perrotta S, Amendola G, Moretti A, Zelante L, Iolascon A. An autosomal dominant thrombocytopenia gene maps to chromosomal region 10p. *Am J Hum Genetics* 1999;65(5):1401–1405. doi:10.1086/302637.
- Pippucci T, Savoia A, Perrotta S, Pujol-Moix N, Noris P, Castegnaro G, Pecci A, Gnan C, Punzo F, Marconi C, et al., Mutations in the 5' UTR of ANKRD26, the ankirin repeat domain 26 gene, cause an autosomal-dominant form of inherited thrombocytopenia. *THC2. Am J Hum Genetics* 2011;88(1):115–120. doi:10.1016/j.ajhg.2010.12.006.
- Noris P, Favier R, Alessi M-C, Geddis A, Kunishima S, Heller P, Giordano P, Niederhoffer KY, Bussel JB, Podda GM, et al., ANKRD26-related thrombocytopenia and myeloid malignancies. *Blood* 2013;122(11):1987–1989. doi:10.1182/blood-2013-04-499319.
- Noris P, Perrotta S, Seri M, Pecci A, Gnan C, Giuseppe L, Pujol-Moix N, Zecca M, Scognamiglio F, De Rocco D, et al., Mutations in ANKRD26 are responsible for a frequent form of inherited thrombocytopenia: analysis of 78 patients from 21 families. *Blood* 2011;117(24):6673–6680. doi:10.1182/blood-2011-02-336537.
- Marconi C, Canobbio I, Bozzi V, Pippucci T, Simonetti G, Melazzini F, Angori S, Martinelli G, Saglio G, Torti M, et al., 5'UTR point substitutions and N-terminal truncating mutations of ANKRD26 in acute myeloid leukemia. *J Hematol Oncol* 2017;10(1):18. doi:10.1186/s13045-016-0382-y.
- Zhang L, Yu J, Xian Y, Wen X, Guan X, Guo Y, Luo M, Dou Y. Application of high-throughput sequencing for hereditary thrombocytopenia in southwestern China. *J Clin Lab Anal* 2021;35(8):e23896. doi:10.1002/jcla.23896.
- Daama SAA, Housawi YH, Dridi W, Sager M, Otieno FG, Hou C, Vazquez L, Kim C, Tian L, Sleiman P, et al., A missense mutation in ANKRD26 segregates with thrombocytopenia. *Blood* 2013;122(3):461–462. doi:10.1182/blood-2013-03-489344.
- Rahman ZA, Miller KC, Jabbour H, Alkhatib Y, Donthireddy V. Outcomes of patients with thrombocytopenia evaluated at hematology subspecialty clinics. *Hematol Oncol Stem Cell Ther* 2021;11:2–9. doi: 10.1016/j.hemonc.2021.01.002.
- Botero JP, Chen D, He R, Viswanatha DS, Majerus JA, Coon LM, Nguyen PL, Reichard KK, Oliveira JL, Tefferi A, Gangat N. Clinical and laboratory characteristics in congenital ANKRD26 mutation-associated thrombocytopenia: a detailed phenotypic study of a family. *Platelets* 2016;27(7):1–4. doi:10.3109/09537104.2015.1129225.
- Necchi V, Balduini A, Noris P, Barozzi S, Sommi P, Di Buduo C, Balduini C, Solcia E, Pecci A. Ubiquitin/proteasome-rich particulate cytoplasmic structures (PaCSs) in the platelets and megakaryocytes of ANKRD26-related thrombocytopenia. *Thromb Haemostasis* 2013;109(2):263–271. doi:10.1160/TH12-07-0497.
- Tsang HC, Bussel JB, Mathew S, Liu Y-C, Imahiyerobo AA, Orazi A, Geyer JT. Bone marrow morphology and disease progression in congenital thrombocytopenia: a detailed clinicopathologic and genetic study of eight cases. *Modern Pathol* 2017;30(4):486–498. doi:10.1038/modpathol.2016.218.
- Zidan NI, AbdElmonem DM, Elsheikh HM, Metwally EA, Mokhtar WA, Osman GM. Relation between mutations in the 5' UTR of ANKRD26 gene and inherited thrombocytopenia with predisposition to myeloid malignancies. An Egyptian study. *Platelets* 2020;32(5):1–9. doi:10.1080/09537104.2020.1854544.
- Husnain M, Wang T, Valdes M, Hoffman J, Lekakis L. Multiple myeloma in a patient with ANKRD26-related thrombocytopenia successfully treated with combination therapy and autologous stem cell transplant. *Case Rep Hematol* 2019;2019:9357572. doi:10.1155/2019/9357572.
- Zaninetti C, Melazzini F, Croci GA, Boveri E, Balduini CL. Extramedullary hematopoiesis: a new feature of inherited thrombocytopenias? *J Thromb Haemost* 2017;15(11):2226–2229. doi:10.1111/jth.13850.
- Boutroux H, Petit A, Auvrignon A, Lapillonne H, Ballerini P, Favier R, Leverger G. Childhood diagnosis of genetic thrombocytopenia with mutation in the ankyrin repeat domain 26 gene. *Eur J Pediatr* 2015;174(10):1399–1403. doi:10.1007/s00431-015-2549-x.
- Botero JP, Oliveira JL, Chen D, Reichard KK, Viswanatha DS, Nguyen PL, Pruthi RK, Majerus J, Gada P, Gangat N, et al., ASXL1 mutated chronic myelomonocytic leukemia in a patient with familial thrombocytopenia secondary to germline mutation in ANKRD26. *Blood Cancer J* 2015;5(5):e315. doi:10.1038/bcj.2015.41.
- Ferrari S, Lombardi AM, Putti MC, Bertomoro A, Cortella I, Barzon I, Girolami A, Fabris F. Spectrum of 5'UTR mutations in ANKRD26 gene in patients with inherited thrombocytopenia: c.-140C>G mutation is more frequent than expected. *Platelets* 2017;28(6):1–4. doi:10.1080/09537104.2016.1267337.
- Marquez R, Hantel A, Lorenz R, Neistadt B, Wong J, Churpek JE, Mardini NA, Shaikat I, Gurbuxani S, Miller JL, et al., A new family

- with a germline *ANKRD26* mutation and predisposition to myeloid malignancies. *Leukemia Lymphoma* 2014;55(12):2945–2946. doi:10.3109/10428194.2014.903476.
26. Diep RT, Corey K, Arcasoy MO. A novel nucleotide substitution in the 5' untranslated region of *ANKRD26* gene is associated with inherited thrombocytopenia: a report of two new families. *Ann Hematol* 2019;98(7):1789–1791. doi:10.1007/s00277-019-03632-y.
 27. Lazaro E, Houssin C, Sentilhes L, Blouin L, Fiore M. Successful management of a pregnant woman with severe *ANKRD26*-related thrombocytopenia and anti-HPA-5b alloimmunization. *Platelets* 2019;31(6):1–3.
 28. Pecci A. Diagnosis and treatment of inherited thrombocytopenias. *Clin Genet* 2016;89(2):141–153. doi:10.1111/cge.12603.
 29. Pecci A, Balduini CL. Inherited thrombocytopenias: an updated guide for clinicians. *Blood Rev* 2020;48:100784. doi:10.1016/j.blre.2020.100784.
 30. Zaninetti C, Santini V, Tiniakou M, Barozzi S, Savoia A, Pecci A. Inherited thrombocytopenia caused by *ANKRD26* mutations misdiagnosed and treated as myelodysplastic syndrome: report on two cases. *J Thromb Haemost* 2017;15(12):2388–2392. doi:10.1111/jth.13855.
 31. Bellissimo DC, Speck NA. RUNX1 mutations in inherited and sporadic leukemia. *Front Cell Dev Biol* 2017;5:111. doi:10.3389/fcell.2017.00111.
 32. Godley LA, Shimamura A. Genetic predisposition to hematologic malignancies: management and surveillance. *Blood* 2017;130(4):424–432. doi:10.1182/blood-2017-02-735290.
 33. Feurstein S, Godley LA. Germline ETV6 mutations and predisposition to hematological malignancies. *Int J Hematol* 2017;106(2):189–195. doi:10.1007/s12185-017-2259-4.
 34. Kikuno R, Nagase T, Ishikawa K, Hirose M, Miyajima N, Tanaka A, Kotani H, Nomura N, Ohara O. Prediction of the coding sequences of unidentified human genes. XIV. The complete sequences of 100 new cDNA clones from brain which code for large proteins in vitro. *DNA Res* 1999;6(3):197–205. doi:10.1093/dnares/6.3.197.
 35. Kim M-S, Pinto SM, Getnet D, Nirujogi RS, Manda SS, Chaerkady R, Madugundu AK, Kelkar DS, Isserlin R, Jain S, et al., A draft map of the human proteome. *Nature* 2014;509(7502):575–581. doi:10.1038/nature13302.
 36. The Uniprot Consortium UniProt: the universal protein knowledge-base in 2021. *Nucleic Acids Res* 2021;49(D1):D480–9. doi:10.1093/nar/gkaa1100.
 37. Lee Y, Ise T, Ha D, Fleur AS, Hahn Y, Liu X-F, Nagata S, Lee B, Bera TK, Pastan I, et al., Evolution and expression of chimeric POTE-actin genes in the human genome. *Proc National Acad Sci* 2006;103(47):17885–17890. doi:10.1073/pnas.0608344103.
 38. Yoonsoo H, Tapan KB, Ira HP, Byungkook L. Duplication and extensive remodeling shaped POTE family genes encoding proteins containing ankyrin repeat and coiled coil domains. *Gene* 2006 Feb 1;366(2):238–245. doi:10.1016/j.gene.2005.07.045.
 39. Yan H, Chen C, Chen H, Hong H, Huang Y, Ling K, Hu J, Wei Q. TALPID3 and *ANKRD26* selectively orchestrate FBF1 localization and cilia gating. *Nat Commun* 2020;11(1):2196. doi:10.1038/s41467-020-16042-w.
 40. Bera TK, Liu X-F, Yamada M, Gavrilova O, Mezey E, Tessarollo L, Anver M, Hahn Y, Lee B, Pastan I, et al., A model for obesity and gigantism due to disruption of the *Ankrd26* gene. *Proc National Acad Sci* 2008;105(1):270–275. doi:10.1073/pnas.0710978105.
 41. Bowler M, Kong D, Sun S, Nanjundappa R, Evans L, Farmer V, Holland A, Mahjoub MR, Sui H, Loncarek J, et al., High-resolution characterization of centriole distal appendage morphology and dynamics by correlative STORM and electron microscopy. *Nat Commun* 2019;10(1):993. doi:10.1038/s41467-018-08216-4.
 42. Bluteau D, Balduini A, Balayn N, Currao M, Nurden P, Deswarte C, Leverger G, Noris P, Perrotta S, Solary E, et al., Thrombocytopenia-associated mutations in the *ANKRD26* regulatory region induce MAPK hyperactivation. *J Clin Invest* 2014;124(2):580–591. doi:10.1172/JCI71861.
 43. Raciti GA, Spinelli R, Desiderio A, Longo M, Parrillo L, Nigro C, D'Esposito V, Mirra P, Fiory F, Pilone V, et al., Specific CpG hyper-methylation leads to *Ankrd26* gene down-regulation in white adipose tissue of a mouse model of diet-induced obesity. *Sci Rep Uk* 2017;7(1):43526. doi:10.1038/srep43526.
 44. Desiderio A, Longo M, Parrillo L, Campitelli M, Cacace G, de Simone S, Spinelli R, Zatterale F, Cabaro S, Dolce P, et al., Epigenetic silencing of the *ANKRD26* gene correlates to the pro-inflammatory profile and increased cardio-metabolic risk factors in human obesity. *Clin Epigenetics* 2019;11(1):181. doi:10.1186/s13148-019-0768-0.
 45. Fournier E, Debord C, Soenen V, Trillot N, Gonzales F, Tintiller V, Terriou L, Derrieux C, Abou Chahla W, Paris C, et al., Baseline dysmegakaryopoiesis in inherited thrombocytopenia/platelet disorder with predisposition to haematological malignancies. *Brit J Haematol* 2020;189(4):e119–22. doi:10.1111/bjh.16543.
 46. Ouchi-Uchiyama M, Sasahara Y, Kikuchi A, Goi K, Nakane T, Ikeno M, Noguchi Y, Uike N, Miyajima Y, Matsubara K, et al., Analyses of genetic and clinical parameters for screening patients with inherited thrombocytopenia with small or normal-sized platelets. *Pediatr Blood Cancer* 2015;62(12):2082–2088. doi:10.1002/pbc.25668.
 47. Ventz R, Hundemer M, Witzens-Harig M, Lehmann B, Felbor U, Najm J. Milde Blutungsneigung bei einer 62-Jährigen mit hereditärer Thrombozytopenie. *Internist (Berl)* 2013;54(6):765–768. doi:10.1007/s00108-013-3284-x.
 48. Kewan T, Noss R, Godley LA, Rogers HJ, Carraway HE. Inherited thrombocytopenia caused by germline *ANKRD26* mutation should be considered in young patients with suspected myelodysplastic syndrome. *J Invest Med High Impact Case Rep* 2020;8:2324709620938941. doi:10.1177/2324709620938941.
 49. Averina M, Jensvoll H, Strand H, Sovershaev M. A novel *ANKRD26* gene variant causing inherited thrombocytopenia in a family of Finnish origin: another brick in the wall? *Thromb Res* 2017;151:41–43. doi:10.1016/j.thromres.2017.01.001.
 50. Tan C, Dai L, Chen Z, Yang W, Wang Y, Zeng C, Xiang Z, Wang X, Zhang X, Ran Q, Guo H. A rare big Chinese family with thrombocytopenia 2: a case report and literature review. *Frontiers Genetics*. 2020;11:340.
 51. Yoshimi A, Toya T, Nannya Y, Takaoka K, Kirito K, Ito E, Nakajima H, Hayashi Y, Takahashi T, Moriya-Saito A, et al., Spectrum of clinical and genetic features of patients with inherited platelet disorder with suspected predisposition to hematological malignancies: a nationwide survey in Japan. *Ann Oncol* 2016;27(5):887–895. doi:10.1093/annonc/mdw066.
 52. Tan C, Dai L, Yang W, Li F, Wang L, Xiao Y, Wang X, Zhang Y, Wang Y, Zeng C, et al. Generation of the human induced pluripotent stem cell line (SHAMUi001-A) carrying the heterozygous c.-128G>T mutation in the 5'-UTR of the *ANKRD26* gene. *Stem Cell Res* 2020;48:102002. doi:10.1016/j.scr.2020.102002.
 53. Minamiguchi H, Kimura T, Urata Y, Miyazaki H, Bamba T, Abe T, Sonoda Y. Simultaneous signalling through c-mpl, c-kit and CXCR4 enhances the proliferation and differentiation of human megakaryocyte progenitors: possible roles of the PI3-K, PKC and MAPK pathways. *Brit J Haematol* 2001;115(1):175–185. doi:10.1046/j.1365-2141.2001.03068.x.
 54. Wahlster L, Verboon JM, Ludwig LS, Black SC, Luo W, Garg K, Voit RA, Collins RL, Garimella K, Costello M, et al., Familial thrombocytopenia due to a structural variant resulting in a WAC-*ANKRD26* fusion transcript. *J Exp Med* 2021;218(6):e20210444. doi:10.1084/jem.20210444.
 55. Acs P, Bauer PO, Mayer B, Bera T, Macallister R, Mezey E, Pastan I. A novel form of ciliopathy underlies hyperphagia and obesity in *Ankrd26* knockout mice. *Brain Struct Funct* 2015;220(3):1511–1528. doi:10.1007/s00429-014-0741-9.
 56. Conduit PT, Wainman A, Raff JW. Centrosome function and assembly in animal cells. *Nat Rev Mol Cell Bio* 2015;16(10):611–624. doi:10.1038/nrm4062.
 57. Evans LT, Anglen T, Scott P, Lukasik K, Loncarek J, Holland AJ. *ANKRD26* recruits PIDD1 to centriolar distal appendages to activate the PIDDosome following centrosome amplification. *Embo J* 2021;40(4):e105106. doi:10.15252/embj.2020105106.
 58. Burigotto M, Mattivi A, Migliorati D, Magnani G, Valentini C, Rocuzzo M, Offerdinger M, Pizzato M, Schmidt A, Villunger A, et al., Centriolar distal appendages activate the centrosome-PIDDosome-p53 signalling axis via *ANKRD26*. *Embo J* 2021;40(4):e104844. doi:10.15252/embj.2020104844.
 59. Matteo B, Luca LF. The PIDDosome: centrosome guardian and backup on the DNA damage response. *Mol Cell Oncol* 2021 May 4;8(3):1893625. doi:10.1080/23723556.2021.1893625.