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Familial Leukemia Associated with Thrombocytopenia

Jakub Trizuljak and Michael Doubek

Abstract

Familial predisposition to leukemia has been known for decades. In some families, this condition is also associated with thrombocytopenia and history of bleeding. Germline mutations in the RUNX1 gene have been proven to cause familial platelet disorder with predisposition to myeloid malignancies (FDPMM). The disease typically presents with mild-to-moderate thrombocytopenia with normal-size platelets, functional platelet defects leading to prolonged bleeding, and an increased risk to develop myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), or T-cell acute lymphoblastic leukemia (T-ALL). In recent years, molecular defects in other genes, such as ANKRD26 and ETV6, have been associated with thrombocytopenia and susceptibility to hematological malignancy as well. In our chapter, we will present a review of up-to-date knowledge on this topic along with several case studies demonstrating the diagnostic process and management of the affected families.

Keywords: AML, familial, RUNX1, ANKRD26, ETV6

1. Introduction

Familial leukemia (e.g., repeated occurrence of hematologic neoplasia in families more often than is expected by chance alone) has been a topic of interest for decades. Almost a hundred years ago, connections between inherited forms of myelodysplastic syndrome (MDS) and myeloid and lymphoid leukemia were established with several constitutional disorders in childhood, such as Fanconi anemia [1]. Since then, a number of additional inherited bone marrow failure syndromes and inherited conditions with predisposition to leukemia were discovered. Repeated occurrence of similar phenotypes, high clinical penetrance for hematologic disorders, and often consanguineous inheritance made identification of the respective genetic causes easier. These conditions are caused by germline mutations (genetic changes which can be carried on to next generations) in genes playing an important role in the development and maintenance of hematopoietic system. Collective effort of many researchers in the past has improved the knowledge about risk for MDS/leukemia, as well as the natural history and clinical outcomes of affected patients [2].

Some of these syndromes present with a distinctive hematological phenotype—thrombocytopenia. Until the end of the last century, only a few forms of inherited thrombocytopenia were known, all of which were extremely rare. Since then, the knowledge of thrombocytopenia has improved, and we presently know at least 26 disorders caused by mutations in 30 genes [3]. It also became quite apparent that in

Myeloid neoplasm classification	Genes involved	Recurrently mutated in sporadic AML, largely initiating or secondary event
Myeloid neoplasma without a preexisting disorder or organ dysfunction	*CEBPA*	Yes, secondary
	DDX41	No
Myeloid neoplasms and preexisting platelet disorders	*RUNX1*	Yes, secondary
	ANKRD26	No
	ETV6	Yes, secondary
Myeloid neoplasm and other organ dysfunction		
Germ line *GATA2* mutation	*GATA2*	Yes, secondary
BM failure syndromes*	*Multiple*	No
Telomere biology disorders	*TERT, TERK*	No
JMML associated with neurofibromatosis, Noonan syndrome or Noonan syndrome-like disorders, Down syndrome	*NF1, PTPN11, CBL, KRAS*	Yes, secondary

* Includes Fanconi anemia (FANCA, FANCB, FANCC, FANCD1 (BRCA1), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM, FANCN (PALB2), FANCO (RAD51C), FANCP (SLX4), FANCQ (ERCC4), FANCR (RAD51), FANCS (BRCA1), FANCT (UBE2T), FANCU, (XRCC2), FANCV (MAD2L2/REV7) and FANCW (RFWD3)), dyskeratosis congenita (DKC1, TERC, TERT, TIN2, NOP10, NHP2), Schwachman-Diamond syndrome (SBDS), Diamond Blackfan anemia (RPS19, RPS24, RPs17, RPL5, RPL11, RPL35A, RPS7, RPS10, RPS26, GATA1), congenital amegakaryocytic thrombocytopenia (MPL), and severe congenital neutropenia (ELA2, GFI1, HAX1).

Figure 1.
Myeloid malignancies with germline predisposition. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia [4].

some families, there is a connection between thrombocytopenia and additional risk of hematological malignancy. Thanks to availability of next-generation sequencing (NGS) technologies, genes associated with hereditary thrombocytopenia and risk of leukemic transformation were successfully identified, notably RUNX1, ETV6, and ANKRD26. These new hereditary syndromes were included in the 2016 revision of World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia [4] **(Figure 1)**.

2. *RUNX1* deficiency (familial platelet disorder with predisposition to myeloid malignancies (FPDMM))

RUNT-related transcription factor 1 (RUNX1) is a master regulator of hematopoiesis [5]. It is involved in the most frequent chromosome translocations in leukemia (i.e., t (12;21)/*RUNX1/ETV6*, t(8;21)/*RUNX1/RUNX1T1*, and t(3;21)/*RUNX1/EVI1*) [6]. Moreover, somatic *RUNX1* mutations have been identified as recurrent abnormalities in myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) [7].

For the first time, germline *RUNX1* mutations were described in 1999 [8]. Individuals carrying germline *RUNX1* mutation may develop familial platelet disorder with predisposition to myeloid malignancies (FPDMM). Characteristic features include (1) thrombocytopenia, (2) functional platelet defects, and (3) an increased risk to develop MDS, AML, or acute T-lymphoblastic leukemia (T-ALL). There is a significant phenotypic heterogeneity. FPDMM (MIM601399) is inherited in an autosomal-dominant mode with incomplete penetrance and variable expressivity [5, 6].

2.1 Diagnostic criteria to identify at-risk individuals

Diagnosis of FDPMM in patients with leukemia carries important clinical implications for the patient but also for her/his family. Recognition of clinical features pointing to this genetic predisposition is crucial. The most important feature is persistent thrombocytopenia or aspirin-like platelet disorder. Pedigree analysis can identify first- or second-degree relatives with higher occurrence of bleeding and hematological malignancies. The bleeding symptoms may be mild or not present. Onset of leukemia varies and spans from infant age to adulthood [9, 10]. In the case of family history of MDS, early-onset leukemia and/or a personal history of bleeding, immune deficiency, or dysmorphic features, genetic counseling is advised [11, 12]. Comprehensive evaluation involves a thorough review of individual's family and personal history, hematologic investigation, and personal risk assessment of likelihood of a hereditary predisposition within his/her family, and if necessary, genetic testing with NGS to determine the possibility of a germline mutation should be offered [13]. We provide an example of a familial case of FDPMM in **Figure 2** [14].

Predictive testing of healthy relatives is advised due to risk of bleeding and leukemia, even in infancy. In the case of individuals with leukemia, where allogenic stem cell transplantation from a HLA-matching sibling donor is the best possible treatment option, mutation screening should be a part of decision-making process, to prevent adverse outcomes after transplantation [15–17].

Due to the advance and widespread use of NGS technologies in diagnosis of myeloid neoplasia in recent years, many individuals at risk are being identified by screening large cohorts of patients. In particular, leukemias with homozygous RUNX1 mutations, biallelic RUNX1 mutations, and trisomy 21 indicate that the patients are likely candidates for FDPMM [18].

2.2 Platelet features

A personal or family history of thrombocytopenia and/or bleeding tendency may be an important pointer to diagnose FDPMM in patient with MDS, AML, or T-ALL. The platelet count is usually mild to moderate and, in some cases, low-normal and even normal. Platelet size is not affected—similar to ETV6- or ANKRD26-related thrombocytopenias, which are also characterized by normal-size platelets [19]. Thrombocytopenia is caused by abnormal megakaryocyte maturation and impaired proplatelet formation. Dysmegakaryopoiesis may be present in bone marrow smears even before leukemic transformation [20].

A functional defect of platelets is present in most, if not all, patients with RUNX1 germline mutations, leading to abnormal secretion and aggregation [21].

The bleeding diathesis is variable within and among families. As some carriers of RUNX1 have mild or none bleeding symptoms, the presence of mutation may go unnoticed, and genetic screening is necessary to determine mutational status.

2.3 Role of *RUNX1* in hematopoiesis

The finding of platelet abnormalities in patients with FDPMM has revealed the essential role of RUNX1 in the megakaryocytic lineage. RUNX1 works as a transcription factor at different stages of megakaryocyte development by regulating the expression of multiple factors relevant to platelet production and function. Reduced expression of RUNX1 target genes, including MPL proto-oncogene, thrombopoietin receptor (MPL), nonmuscle myosin IIA/myosin heavy chain 9 (MYH9) and its regulatory chain MLC2, arachidonate 12-lipoxygenase (ALOX12), and NFE2, has been shown to cause the defect in platelet number and function in FDPMM [22, 23]. What is more, increased levels
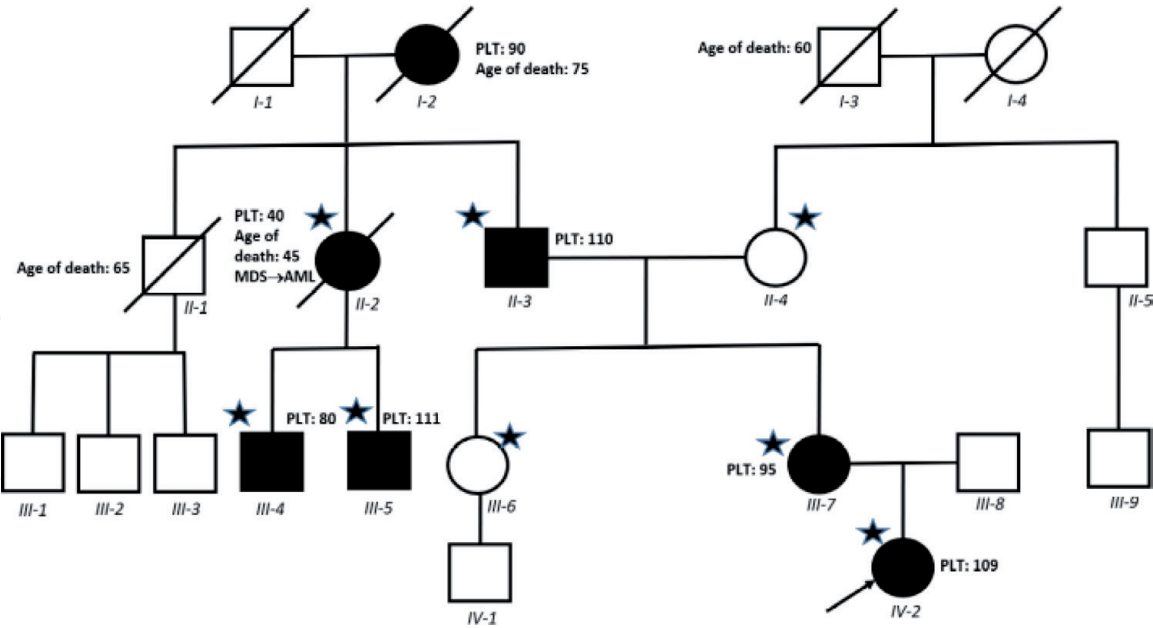
Figure 2.
Pedigree of a family with thrombocytopenia and predisposition to myeloid malignancies. We identified a family with platelet disorder and predisposition to myeloid malignancies. Using exome sequencing of samples of eight family members, we identified a pathogenic frameshift variant c.866delG (p.Gly289Aspfs*22) in exon 8 of RUNX1 gene, resulting in a premature stop codon. The mutation occurs within the transactivation domain of RUNX1. One of the affected individuals developed myelodysplastic syndrome, which progressed to acute myelogenous leukemia. Platelet count (PLT) reported in ×109/L, samples analyzed by exome sequencing marked with an asterisk (*), age of death if known [14].

of nonmuscle myosin IIB (MYH10), which is physiologically repressed by RUNX1, contribute to thrombocytopenia by blocking megakaryocyte polyploidization [24].

RUNX1 is a master regulator in hematopoietic differentiation. It plays a role in the first wave of hematopoiesis producing primitive erythroid cells and mega-karyocytes. By enhanced expression of CEBPE, it negatively regulates myeloid progenitors and induces granulocytic differentiation. RUNX1 also regulates cell adhesion to the bone marrow niche [25]. After dimerizing with core-binding factor beta (CBFB), RUNX1 binds to promotor regions of several transcription factors like PU.1, regulating their expression. Binding to DNA and CBFB occurs in the highly conserved Runt homology domain (RHD) at the N-terminal region. Transactivation occurs at the C-terminal part of the molecule [26].

2.4 Phenotype/genotype correlation

Most RUNX1 mutations lie in the Runt homology domain region (RHD) [1]. Causative mutations are deleterious—most often frameshift, nonsense, or in/del mutations that result in premature protein truncation or nonsense-mediated decay of mRNA. Missense mutations may be present as well. In these cases, it may be hard to determine the pathogenicity of found variants. Here, segregation analyses and functional analyses are needed to confirm the effect of the variants for patho-genesis. Loss of function mutations in RHD, located in the N-terminal part of the protein, impairs normal RUNX1 function by hindering dimerization and DNA binding. These, as well as mutations in the 5′ regulatory region cause haploinsuf-ficiency [27]. Missense mutations in RHD and nonsense and frameshift mutations in the C-terminal domain may lead to dominant-negative effects [10].

What is more, there are inherited structural rearrangements involving RUNX1: FDPMM can also be caused by small deletions involving a few base pairs or single exons of the gene and large deletions leading to loss of the complete coding regions.

Deletions of large parts of the long arm of chromosome 21 cause a contiguous gene with various clinical signs, e.g., facial dysmorphism, mental retardation, thrombocytopenia, and increased risk of myeloid malignancies. These large deletions can be reliably detected by array comparative genomic hybridization (CGH)/single-nucleotide polymorphism (SNP) arrays [11, 12].

There seems to be a higher risk of leukemic transformation in the case of dominant-negative mutations of RUNx1 as compared to loss-of-function mutations. Both types of alterations lead to thrombocytopenia phenotype, but only dominant-negative mutations enhance the proliferation rate and clonogenic potential [28]. In the case of haploinsufficiency, biallelic or second-hit mutations are needed to trigger the leukemic transformation.

Unfortunately, there is no clear phenotype/genotype correlation. Within one family, members carrying the same mutation may present with different clinical signs and severity of symptoms. Some carriers develop only mild thrombocytopenia, while others suffer from myeloid neoplasms [29].

2.5 Risk of malignancy and second-hit mutations in RUNX1 deficiency

The risk of malignant transformation into MDS or AML is estimated to be 30–40% [16]. Patients carrying dominant-negative RUNX1 mutations have a higher risk of malignant transformation. The spectrum of malignancies involves AML of various French-American-British subtypes and MDS (refractory anemia with excess blasts, chronic myelomonocytic leukemia and hypoplastic MDS with myelofibrosis). In some cases T-cell ALL has also been described. In the case of MDS/AML, age of onset is at an average of 33 years with a wide age range, while in T-cell ALL, it usually occurs at a younger age [13, 24].

During the course of the disease, the second allele may be inactivated, as expected for tumor suppressor genes according to two-hit hypothesis. Nowadays, there are no definitive answers to what triggers the malignant transformation in RUNX1 germline mutation carriers. However, clonal hematopoiesis may be present even in asymptomatic mutation carriers, preceding overt MDS/AML or FDPMM [30].

Carriers of RUNX1 germline mutations need additional genetic events to develop hematological neoplasm. Often, biallelic alterations of RUNX1 are found, due to secondary RUNx1 mutations or acquired trisomy 21 resulting in the duplication of the mutated allele [31]. RUNx1 mutations are associated with MLL partial tandem duplications, FLT3-ITD, IDH1/2, RAS mutations, and ETV6 rearrangements. These often occur in therapy-related AML [32]. Recently, malignant transformation was reported to be mediated by recurrent somatic mutations in CD25C gene in up to a half of a Japanese patient cohort with RUNX1-related myeloid neoplasia. Next-generation sequencing allows detection of additional mutations in known AML drivers, such as ASXL1, TET2, IDH1, CEBPD, RB1, MLI2, FLT3-ITD, WT1, and SRSF2 [33, 34].

2.6 Clinical management

Treatment of RUNX1-related AML or MDS follows standard protocols. If a disease-causing germline mutation is known in the family, it is important to prevent hematopoietic stem cell transplantation from a sibling or other relative.

In families with high-penetrance mutations, regular clinical examinations including differential blood count are advised. In case of suspicious clinical symptoms or cytopenias, bone marrow aspiration or biopsy with morphological, cytogenetic, and molecular genetic investigations should be discussed. Using new NGS technologies, it is possible to follow up clonal hematopoiesis [30].

2.7 Conclusion

RUNX1 deficiency is a myeloid malignancy predisposition syndrome with high clinical penetrance and variable expressivity of its phenotypic effects. An aspirin-like platelet and mild-to-moderate thrombocytopenia are present in most of the patients. The presence of possible RUNX1 germline mutations should be part of decision-making process in management of HSCT and donor choice in MDS/AML. Follow-up of asymptomatic mutation carriers is necessary.

3. ETV6-related thrombocytopenia with propensity to hematological malignancies

ETV6 was originally discovered in a leukemia-associated chromosomal translocation [35] and has subsequently been identified as a fusion partner in more than 30 chromosomal translocation oncogenes [36]. ETV6 is a transcriptional repressor that binds DNA via a C-terminal DNA-binding domain, highly conserved among ETS-family transcription factors [37]. The ETV6 N-terminal pointed (PNT) domain mediates self-association and frequently contributes to fusion proteins as the partner of tyrosine kinases [38]. Loss of ETV6 has firmly been implicated in the pathogenesis of ETV6-RUNX1(TEL-AML1)-associated childhood leukemia as there is invariably biallelic loss of ETV6 due to deletions of the second (nontranslocated) ETV6 allele [39].

More recently, genome-wide investigations have uncovered that ETV6 is subject to heterozygous mutations in hematologic malignancies, including myelodysplastic syndrome (MDS) [10, 11], acute myeloid leukemia (AML) [40], early T-cell precursor acute lymphoblastic leukemia (T-ALL) [41, 42], high-risk B-ALL [43], and diffuse large B-cell lymphoma (DLBCL) [44]. It remained unclear whether and how loss of ETV6 contributes to leukemogenesis.

Now a number of recent studies have expanded our knowledge. The initial report from Zhang et al. identified the link between heterozygous germline ETV6 mutation to dominantly inherited thrombocytopenia and predisposition to hematological malignancies [45]. Subsequent studies extended these findings to additional families with unique ETV6 germline mutations and predisposition to malignancy [46, 47]. With one exception, all of the germline mutations cluster within the highly conserved ETS domain. The only mutation outside the ETS domain, P214L, was repeatedly identified in family studies.

3.1 Diagnostic criteria to identify at-risk individuals

Diagnosis of ETV6-related thrombocytopenia is paramount due to clinical implications for the patient. The most important clinical feature is thrombocytopenia with normal-sized platelets. Sometimes, large mean corpuscular volume (MCV) of red blood cells is reported. In family history, individuals with occurrence of bleeding and hematological malignancies are identified. Bleeding symptoms are variable. No recurrent extra-hematologic abnormalities have been identified, though in some families, solid tumors may occur [45].

Genetic counseling, comprehensive evaluation of individual's family and personal history, hematologic investigation, personal risk assessment of likelihood of a hereditary predisposition within his/her family, and, if necessary, genetic testing with NGS are advised. In the case of a found mutation, predictive testing of healthy relatives is necessary to identify at-risk individuals [13]. We provide an example of a familial case of ETV6 deficiency in **Figure 3** [47]. In cases when allogenic

hematopoietic stem-cell transplantation is considered in a patient with leukemia and ETV6 mutation, possible sibling donors must be tested to avoid the risk of relapse and transplant-related morbidity and mortality.

3.2 Platelet features

All affected pedigrees with ETV6 germline mutations have a highly penetrant autosomal-dominant pattern of thrombocytopenia. Severity of thrombocytopenia is highly variable. Many patients have mild thrombocytopenia with platelet counts ranging between 100 and 150×10^9/L, while others had platelet counts ⁵$50 \times 10^9$/L. Severe thrombocytopenia ⁵$20 \times 10^9$L is seen rarely in the absence of myelodysplastic syndrome [46]. Bleeding symptoms reported are generally mild including petechiae, ecchymoses, epistaxis, gum bleeding, easy bruising, and menorrhagia. Platelet size is generally normal, though macrothrombocytopenia may be seen in a subset of patients.

Hemoglobin is normal in most patients. Erythrocyte mean corpuscular volume (MCV) is generally normal or increased. Neutrophil counts are normal. Examination of bone marrow reveals frequent immature hypolobulated megakaryocytes, mild dyserythropoiesis, and mild hypolobulation and hypogranulation of myeloid cells [48].

3.3 Risk of malignancy

A substantial number of patients carrying ETV6 germline mutation develop hematological malignancies during their lifetime. The risk of leukemic transformation is estimated to be up to 25–40%; the age of onset is highly variable (8–82 years). The spectrum of malignancies involves acute lymphoblastic leukemia (ALL) and myeloid malignancies including MDS, AML, chronic myelomonocytic leukemia (CMML), myeloproliferative disorders (typically polycythemia vera), and multiple myeloma. Special attention was brought to relationship between germline ETV6 mutations and childhood ALL. Targeted sequencing of
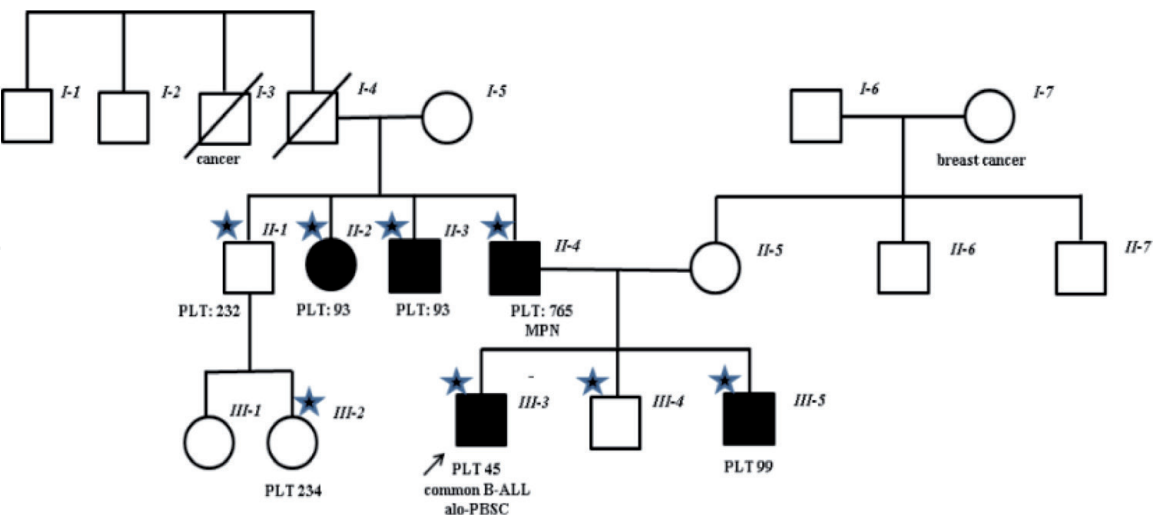
Figure 3.
Pedigree of a family with thrombocytopenia and occurrence of lymphoid and myeloid malignancies. We identified a family with autosomal dominant thrombocytopenia, high erythrocyte mean corpuscular volume (MCV), occurrence of B cell-precursor acute lymphoblastic leukemia (ALL) and myeloproliferative neoplasm (MPN). Whole-exome sequencing identified a heterozygous single-nucleotide change in ETV6 (ETS variant 6), c.1138T>A, encoding a p.Trp380Arg substitution in the C-terminal DNA-binding domain, segregating with thrombocytopenia and elevated MCV. The role of Trp380 is structural, being surrounded by hydrophobic residues in the domain hydrophobic core. Its substitution by an arginine will therefore severely destabilize the domain structure. Platelet count (PLT) reported in ×109/L, samples analyzed by exome sequencing marked with an asterisk [47].

a large cohort of childhood ALL patients revealed 31 leukemia-associated ETV6 exonic variants [49]. All variants in this study were absent in control population. About 48% of found variants were found in the ETS DNA-binding domain and were predicted to be deleterious. Children with ETV6 variants were older at diagnosis (median 10.2 years) than those without ETV6 variants (4.7 years). There was no association between ETV6 mutation status and early treatment response or risk of relapse.

In some families, a few sold tumors have been reported: colorectal carcinoma, breast cancer, renal cell carcinoma, and tumor of the central nervous system. Further investigation is needed to understand the role of ETV6 in solid tumors [45, 49, 50].

3.4 Mutation spectrum

The mutation types in ETV6-related thrombocytopenia with predisposition to malignancies include nonsense, missense, splice site, and frameshift variants. The majority of mutations cluster within the ETS DNA-binding domain and are predicted to be deleterious. The p214L mutation, which resides in the linker region, has been recurrently identified in different families [45, 49].

3.5 Second-hit mutations in ETV6 deficiency

The development of leukemia with variable latency and incomplete penetrance suggests a need for further somatic mutations. Studies did not reveal mutations in the remaining wild-type ETV6 allele in most cases. Such examples are more of an exception. Acquisition of somatic defects in other genes, such as RUNX1, BCOR, and KRAS, is more prominent. The role of additional mutations in malignant transformation remains to be determined [45].

3.6 Molecular structure and role of ETV6

ETV6 is a part of a 26-member family of transcriptional regulators, defined by a highly conserved 85-amino-acid residue that mediates binding of target DNA. Different ETS factors can replace each other in the context of overexpression in vitro but exhibit functional diversity and individual specificity in DNA binding beyond the core motif. ETV6 has the capacity to form polymers with head-to-tail binding of two different protein surfaces within its PNT domain [51].

The primary function of ETV6 is a transcriptional repressor. The PNT domain-mediated multimerization is required for high affinity DNA binding. Truncated ETV6 proteins resulting from frameshift mutations retaining either the PNT domain or the ETS domain were shown to exhibit a dominant-negative activity. This was also demonstrated for the familial germline mutations. This may suggest that the pathogenic activity of ETV6 mutations not only includes loss of function but also interferes with the wild-type allele [40, 52, 53].

ETV6 also plays an important role in embryonic development. Homozygous ETV6 germline disruption results in embryonic lethality in mice studies [54]. ETV6 is required for survival of hematopoietic stem cells in the bone marrow. It also promotes the late phases of megakaryopoiesis. Heterozygous disruption of ETV6 in mice is not associated with obvious phenotypes, implying the dominant-negative effect of germline mutations found in affected families: complete loss of ETV6 is lethal, but development of abnormalities requires more than heterozygous loss [55, 56].

3.7 Clinical management

Treatment of ETV6-related leukemia does not differ from standard protocols. As in FDP-MM, if a disease-causing germline mutation is known in the family, it is necessary to test siblings, as HSCT from a sibling carrier of ETV6 pathogenic variant should be avoided. Family members should be tested, and regular follow-up of mutation carriers including differential blood count is advised. Bone marrow aspiration and/or biopsy with thorough cytogenetic/molecular genetic investigation may be necessary in case of additional cytopenias or other suspicious clinical symptoms [13].

3.8 Conclusion

Discovery of familial ETV6 germline mutations has established its clinical significance as a cause of thrombocytopenia, as well as a major cancer predisposition gene, associated with a substantial number of childhood B-ALL cases as well as myeloid malignancies. However, our understanding of the clinical impact of ETV6 mutations and physiological role of ETV6 remains incomplete. More work is needed to understand the molecular pathology of the mutations and stratify the risk of affected individuals.

4. ANKRD26-related thrombocytopenia

Thrombocytopenia 2 (THC2 MIM 188000) is one of the rarest forms of autosomal-dominant thrombocytopenia. It has so far been reported only in 21 families across the world [57]. The THC2 locus was mapped to chromosome 10p11.1-p12 through linkage analysis in two independent studies [58, 59]. In the original studies, two missense changes in different linked genes were found to be causative of the disease: c.501G > C (p.Glu167Asp) and c.22 C > T (p.his8Tyr). Another study identified pedigrees with six additional ANKRD26 mutations, segregating with thrombocytopenia. All of them were located in a stretch of 19 nucleotides of the 5′ UTR that is highly conserved in evolution. These findings associate ANKRD26 5′ UTR mutations with thrombocytopenia [60]. Further reports extended the number of known families to 21 [61]. The abovementioned studies also found that the number of hematologic malignancies was higher than expected.

4.1 Diagnostic criteria, platelet features

THC2-affected individuals have a degree of thrombocytopenia ranging from mild to severe and suffer from a mild bleeding diathesis. Major bleeding events are rare. Platelets are normal-sized and morphology does not reveal any defects. Examination of bone marrow shows dysmegakaryocytopoietic phenomena. No other changes in blood count, e.g., anemia and neutropenia, were reported [60].

4.2 Risk of malignancy

A comprehensive study of 118 subjects affected with THC2 identified 10 patients who developed myeloid malignancies: four acute myeloid leukemias (AML), four myelodysplastic syndromes, and two chronic myeloid leukemias (CML). Cumulative incidence of hematological malignancies in this subset of patients is 8.47%. The incidence of lymphoproliferative disorders and nonhematologic cancers was not higher than expected. Available data are compatible with the hypothesis

that ANKRD26-related thrombocytopenia predisposes to myeloid malignancy. However, penetrance for neoplasia is incomplete, and other genetic or environmental factors must contribute to development of these disorders [57].

4.3 Molecular genetics

ANKRD26 is the ancestor of a family of primate-specific genes termed POTE (prostate-ovary-testes- and placenta-expressed genes) whose expression is restricted to several normal to a few normal tissues and a larger number of malignancies, such as breast cancer. ANKRD26 is expressed also in megakaryocytes and to lesser extent erythroid cells [62, 63].

The functional role of ANKRD26 is unknown. Deleterious mutations of aNKRD26 in animal studies do not cause thrombocytopenia. This evidence suggests that THC2 is more likely to be caused by gain-of-function mutations rather than haploinsufficiency. It is suspected that mutations in the 5′ UTR interfere with mechanisms controlling the expression of ANKRD26 and affect megakaryopoiesis and platelet production, possibly by induction of apoptosis [60, 64].

4.4 Clinical management

As in the abovementioned entities, screening for ANKRD26 mutations must be a part of diagnostic process in hereditary thrombocytopenia and familial myeloid leukemia. Follow-up of asymptomatic mutation carriers in regular intervals including peripheral blood count and smear is necessary. The presence of ANKRD26 germline mutations in acute leukemia may also play a part in HSCT-related questions.

4.5 Conclusions

ANKRD26 is a rare form of inherited thrombocytopenia with low risk of bleeding and predisposition to myeloid malignancies. Recognition of this disorder is important in differential diagnosis of hereditary thrombocytopenia and proper management of affected subjects.

5. Further candidate genes

There are several genes associated with inherited bone marrow failure syndromes (IBMFS) and thrombocytopenia, notably MPL, THPO, HOXA11, MECOM, and RBM8A, as well as mutations in genes for X-linked thrombocytopenia and immune deficiency (GATA1, WAS) [65]. These clinical entities present with thrombopenia or pancytopenia and, in some cases, dysmorphic features. The IBMFS are complex disorders unified by development of bone marrow failure and increased risk of leukemic transformation. In some IBMFS, the steps toward leukemic transformation are better understood. In others, there is still much to learn. The estimated risk of malignancy in the abovementioned entities requires additional research.

MYH9 mutations result in congenital macrothrombocytopenia and predispose to kidney failure, hearing loss, and cataracts. There are a few published cases of germline mutations of MYH9 with myeloid malignancy [66]. Somatic expression of MYH9 has impact on overall survival in patients with AML [67]. However, additional studies on larger patient populations are needed to confirm this suspicion.

6. Conclusion

In this chapter, we have summarized current knowledge of familial syndromes with thrombocytopenia and predisposition to hematologic malignancies. These rare disorders must be a part of differential diagnosis of (1) unexplained or familial thrombocytopenia, (2) myeloid malignancies with familial occurrence, and (3) bone marrow failure syndromes. Only a correct diagnosis with up-to-date hematological and molecular diagnostics can lead to proper follow-up of affected individuals and families. Personalized risk assessment must be made; and in the case of a familial germline mutation, genetic reproductive consultation should be offered.

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Conflict of interest

The authors declare no conflict of interest.

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