



ETV6-related thrombocytopenia and leukemia predisposition

Jorge Di Paola¹ and Christopher C. Porter²

¹Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO; and ²Department of Pediatrics, Emory University School of Medicine, Atlanta, GA

Germ line mutations in *ETV6* are responsible for a familial thrombocytopenia and leukemia predisposition syndrome. Thrombocytopenia is almost completely penetrant and is usually mild. Leukemia is reported in ~30% of carriers and is most often B-cell acute lymphoblastic leukemia. The mechanisms by which *ETV6* dysfunction promotes thrombocytopenia and leukemia remain unclear. Care for individuals with *ETV6*-related thrombocytopenia and leukemia predisposition includes genetic counseling, treatment or prevention of excessive bleeding and surveillance for the development of hematologic malignancy. (*Blood*. 2019;134(8):663-667)

Introduction

It has become clear that a significant fraction of hematologic malignancies (HMs) arise in individuals with germ line alterations in cancer predisposition genes. This is highlighted by the inclusion of myeloid neoplasm with germ line predisposition in the 2016 World Health Organization's classification of myeloid leukemia.¹ Predisposition to HMs can be associated with increased risk of leukemia only or of solid tumors and leukemia or with systemic syndromes.² A fourth group at increased risk of leukemia includes those with mutations in genes that also lead to thrombocytopenia and/or platelet function abnormalities. The purpose of this *Blood* Spotlight is to concisely review *ETV6*-related thrombocytopenia and leukemia predisposition disorder, which arises as a result of germ line mutations in *ETV6*.

Clinical features

ETV6-related thrombocytopenia and leukemia predisposition was first recognized in pedigrees with an autosomal dominant disorder of thrombocytopenia.^{3,4} Subsequent reports confirmed near-complete penetrance of thrombocytopenia,⁵⁻⁷ although some carriers with normal platelet counts have been reported.⁸⁻¹¹ The thrombocytopenia is usually mild to moderate, with most patients having platelet counts $>75 \times 10^9/L$. Complete blood counts (CBCs) usually show normal white blood cell counts and hemoglobin concentrations, with variably high mean corpuscular volumes and, less consistently, low mean platelet volumes (Figure 1; supplemental Table 1, available on the *Blood* Web site).

In addition to thrombocytopenia, carriers of *ETV6* mutations have variable bleeding tendencies, with some patients not experiencing any bleeding despite low platelet counts and other patients having more bleeding than expected for mildly decreased platelet counts. Some have been reported to have abnormal platelet aggregation despite no major differences in platelet membrane receptor distribution (supplemental Table 1).

Platelets from patients with *ETV6* mutations exhibit abnormal platelet spreading on fibrinogen surfaces and abnormal clot retraction, suggesting a defect in platelet outside-in signaling.^{5,6} Bone marrow aspirates and biopsies from those without leukemia reveal dyserythropoiesis, megakaryocyte hyperplasia, and hypolobulated small megakaryocytes (Figure 1).³⁻⁵

Among the 96 cases from 23 pedigrees that have been reported and confirmed to carry an *ETV6* mutation, 29 (30.2%) were diagnosed with HMs (supplemental Table 1). B-cell acute lymphoblastic leukemia (B-ALL) is the most common malignancy, accounting for approximately two-thirds of cases. Furthermore, in a study of >4000 children with ALL, germ line *ETV6* variants were identified in almost 1%.¹⁰ Individuals with germ line *ETV6* variants were more likely to have hyperdiploid leukemia, similar to recent findings with germ line IKZF1 variants, and were significantly older at diagnosis than those without.^{10,12} Other reported HMs in mutation carriers include myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), mixed-phenotype acute leukemia, diffuse large B-cell lymphoma, polycythemia vera, and multiple myeloma. Cooccurring mutations include those in *BCOR*, *RUNX1*, *KMT2A*, *PAX5*, and *EPOR*, but the extent to which these specifically cooperate with *ETV6* dysfunction remains to be demonstrated.^{3,4} There may also be an increased risk of solid tumors, because at least 7 carriers have had various benign and malignant solid tumors at ages <50 years, and a common polymorphism in *ETV6* is associated with an increased risk of colorectal carcinoma.¹³ Other nonhematologic associations are generally not shared across pedigrees.^{3,7,10} Type of mutation does not seem to influence the penetrance of malignancy.

ETV6 structure and function

ETV6 is a member of the ETS family of transcription factors encoded by the ETS variant 6 gene (*ETV6*), located on chromosome 12p13.2. *ETV6* functions primarily as a transcriptional

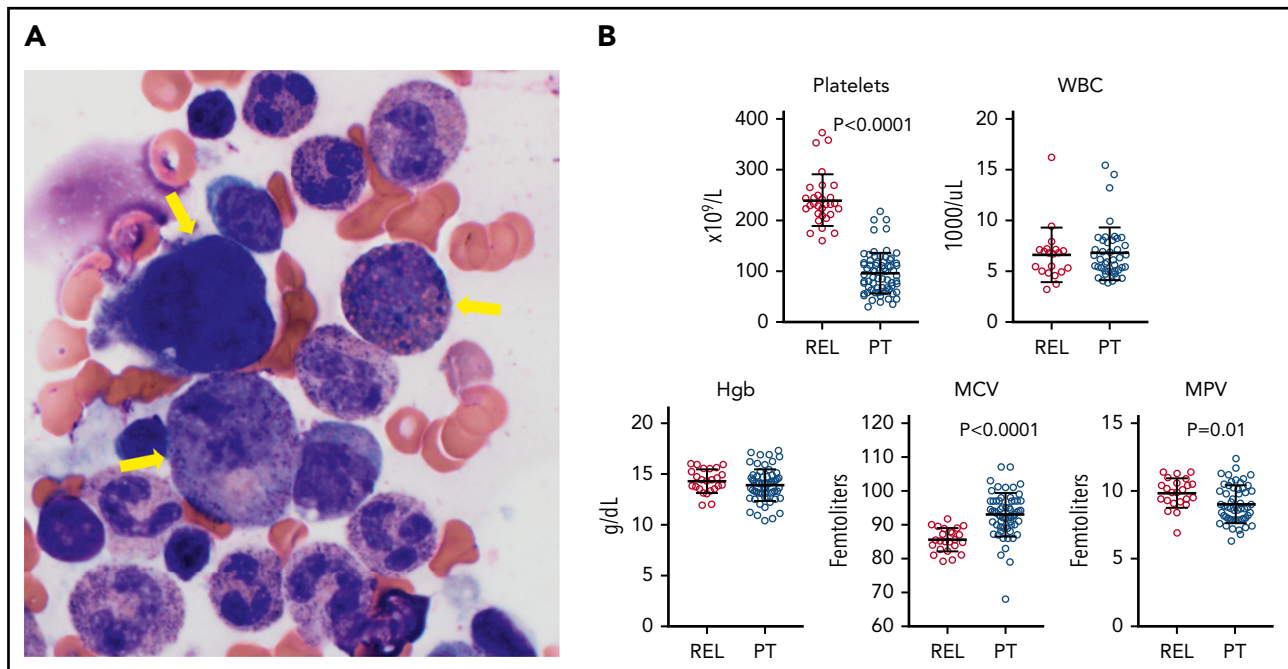


Figure 1. Abnormal bone marrow histology and CBCs in patients with ETV6-related thrombocytopenia and leukemia predisposition. (A) Abnormal cellular features (yellow arrows) with hyperchromatic small megakaryocytes, disseminated toxic granulations, and dysplastic eosinophils (magnification $\times 100$; Wright-Giemsa stain). (B) Platelet count, white blood cell (WBC) count, hemoglobin (Hgb), mean cell volume (MCV), and mean platelet volume (MPV) in patients (PT) with germ line mutations in ETV6, as compared with related individuals (Rel) without mutation (Student t test).^{3-6,9,10}

repressor in complex with SIN3A, NCOR, and HDAC3.¹⁴⁻¹⁶ The 57-kDa ETV6 protein has highly conserved PNT and ETS DNA-binding domains (Figure 2). PNT is essential for homo- and heterooligomerization, whereas the ETS domain is essential for DNA binding at the core 5'GGA(A/T)3' sequence recognized by other ETS family members.¹⁷ The 2 domains are joined by a central linker domain,¹⁴ known to be involved in nuclear export,^{18,19} binding of NCOR and HDAC3,¹⁶ and transcriptional repression.²⁰

ETV6 is highly expressed in early hematopoietic progenitor cells (HPCs) and is essential for hematopoiesis in the bone marrow.²¹ Complete knockout of *Etv6* was lethal to murine embryos by E11.5 because of a yolk sac angiogenesis defect,²² whereas targeted disruption revealed defects in hematopoiesis from bone marrow but not fetal liver.^{23,24} More specifically, conditional knockout of *Etv6* impaired early HPC numbers and function but had little effect when deleted in committed lymphoid progenitors. In contrast, knockout of *Etv6* in megakaryocyte progenitors led to dramatic decreases in platelet counts, suggesting a megakaryocyte differentiation and maturation defect.²³ Although ETV6 has been characterized as a transcriptional repressor, only a few transcriptional targets of ETV6 have been reported,²⁵⁻²⁷ and interestingly, the megakaryocyte/platelet glycoprotein 1b α (GP1b α) and glycoprotein IX (GPIX) are among them.^{28,29} Additionally, ETV6 dimerizes with the ETS transcription factor FLI1, which is known to be involved in megakaryopoiesis,²⁸ suggesting that abnormal interactions between ETV6 and FLI1 contribute to thrombocytopenia.

ETV6 is involved in the most common somatic translocation in childhood B-ALL, resulting in the chimeric fusion protein ETV6-RUNX1, in up to 25% of cases.³⁰ In these cases, the other ETV6

allele is often mutated or deleted subsequent to the translocation, implicating a tumor-suppressive function for ETV6, which is supported experimentally.^{27,31-34} Somatic point mutations or deletions are also recurrently found in high-risk B-ALL,³⁵⁻³⁸ immature T-cell ALL,^{39,40} and, less frequently, MDS/AML,⁴¹⁻⁴³ further underscoring the importance of ETV6 in leukemogenesis.

Molecular and cellular consequences of ETV6 dysfunction

A majority of germ line mutations in ETV6 are missense variants in the DNA-binding domain of the protein (Figure 2), and most are private within pedigrees. However, there are 5 pedigrees reported with a recurrent mutation in the central domain (P214L), and some amino acids have multiple variants reported (Y401H/N, R369Q/W). The R369Q and R399C variants have reduced DNA binding,³ and all tested variants have impaired transcriptional repression and/or dominant-negative activity when tested with wild-type (WT) ETV6.^{3-5,7} Deletions have also been described, 3 of which alter splice sites and are predicted to result in protein truncation (K384fsTer and 2 resulting in N385fsTer).^{6,7,11,44} All tested variants have reduced nuclear and increased cytoplasmic localizations of ETV6.^{3,4,7} This suggests that ETV6 variants may impair WT ETV6 function in part by oligomerizing with and sequestering WT ETV6 out of the nucleus, although altered subcellular localization has yet to be demonstrated with endogenously expressed ETV6. Reduced association with corepressors may also alter transcriptional function, as demonstrated for the A377T and Y401N variants.⁵

Global patterns of gene expression are affected by the expression of mutant ETV6.^{3,4} In particular, changes in expression

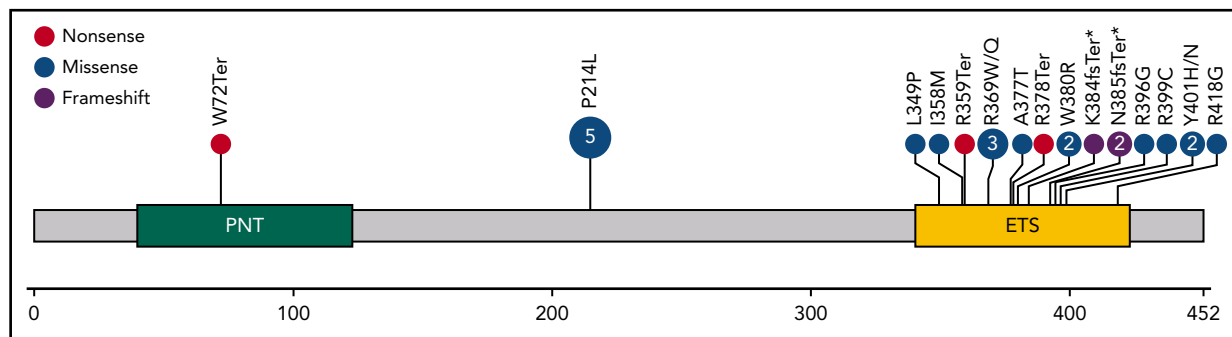


Figure 2. Schematic of ETV6 protein with functional domains and location of germ line mutations from 23 reported pedigrees. The number of families with alterations at the site is indicated in the circles if >1. A deletion that includes all of exon 2 has also been reported.⁴⁴ *Germ line deletions in ETV6 involving splice sites.

levels of genes involved in platelet biogenesis were pronounced, including MYL9, VWF, and GP9. Importantly, platelets from individuals with ETV6 mutations have decreased expression of CDC42 and RHOA, critical regulators of cytoskeletal dynamics in platelets.⁵ Interestingly, the ETV6 p.P214L platelet transcriptome showed an increase in erythroid-specific transcripts and decrease in platelet-specific transcripts as compared with unaffected relatives. The downregulation of platelet-specific genes suggests a function of ETV6 beyond direct transcriptional repression, perhaps by performing a yet-to-be-identified role as a transcriptional activator, showing lineage specificity with a repressive role in erythropoiesis and more permissive role in megakaryopoiesis, or affecting other transcription factor complexes. In accordance with these findings, we have shown an abundance of immature hypolobulated megakaryocytes in the bone marrow of patients with the p.P214L mutation,⁴ and megakaryocytes expressing ETV6 variants are smaller and form fewer proplatelets, whether patient derived or exogenously expressed.⁴⁻⁶

Management of patients with germ line ETV6 mutations

Recommendations from experts⁴⁵⁻⁴⁷ and consensus guidelines⁴⁸ for the care of children and adults with an inherited thrombocytopenia and leukemia predisposition syndrome have been proposed. The differential diagnosis for suspected inherited thrombocytopenia and leukemia predisposition includes germ line mutation in ETV6, as well as RUNX1 and ANKRD26.² Once the diagnosis has been made, management includes identifying related carriers, treatment and/or prevention of excessive bleeding, consideration of surveillance for the development of HMs, particularly MDS, and treatment of HMs, possibly including hematopoietic stem cell transplantation (HSCT). When possible, referral to a center with experience in managing higher volumes of patients with leukemia predisposition syndrome is optimal.^{45,48} Genetic counseling plays a critical role in the management of individuals with germ line ETV6 variants.⁴⁹ Of particular importance is the counseling of siblings who may carry the same mutation and who may be considered as donors for HSCT.

Management of bleeding risk in individuals with ETV6 germ line mutation begins with a thorough assessment of personal and family bleeding histories, platelet count, and, if available, platelet aggregation studies. Because bleeding is usually

mild, observation may be sufficient, whereas local measures, antifibrinolytic agents, and desmopressin can be considered if bleeding is more significant. Acute bleeding may be managed with platelet transfusions, but such transfusions are reserved for episodes of moderate to severe bleeding to mitigate the risk of alloimmunization, particularly in women of childbearing age.⁴⁷ All these therapies can be used to prevent bleeding during hemostatic challenges such as surgery.

Surveillance for HMs can be achieved through serial measurement of CBC with differential (CBCd) and bone marrow aspirate and biopsy (BMA/Bx), although the benefit of doing so has yet to be demonstrated. CBCd every 3 to 6 months and BMA/Bx yearly has been suggested, but the burden of such evaluations must also be considered, particularly for young children and for a syndrome in which acute leukemia is more common than MDS and less likely to be detected before clinical presentation.^{45,46,48} BMA/Bx should include morphology, cytogenetics, fluorescence in situ hybridization, and molecular studies, which are particularly useful when the marrow morphology is abnormal because of the underlying disorder rather than the evolution of MDS/AML. Additional BMA/Bx should be considered in individuals with changes in CBCd that persist for 2 to 4 weeks.

Whether individuals with ETV6 deficiency disorder have different outcomes associated with leukemia compared with those with sporadic disease, including survival as well as immediate and late adverse effects of therapy, remains to be determined. These individuals are at greatest risk for B-ALL, the prognosis of which is excellent in childhood, and children with germ line ETV6 mutation and ALL had outcomes similar to those of children with germ line WT ETV6.¹⁰ Conversely, the prognosis for children and adults with MDS/AML is guarded, and hypothetically, the risk of a distinct second primary malignancy remains in the absence of HSCT, as a result of the ongoing presence of ETV6 mutations in HPCs. Therefore, consultation with a specialist in HSCT early in the course of HMs should be considered. Potential related donors should be counseled and tested because of the risk of donor-derived leukemia.^{50,51}

Future directions

As with all newly defined rare diseases, there is much work to be done to improve the understanding and management of ETV6-related thrombocytopenia and leukemia predisposition. Critical

in this regard is increased awareness among clinicians about this and other inherited thrombocytopenia and leukemia predisposition syndromes, as well as access to high-quality diagnostic laboratories. There is increasing availability of multigene panel testing for cancer predispositions and platelet disorders, but not all include *ETV6*. Furthermore, optimal testing for germ line mutations predisposing to leukemia is obtained from cultured fibroblasts⁴⁶; however, this type of testing is not offered by many laboratories. A major challenge for diagnostic laboratories and clinicians is the classification of variants, which is especially difficult for rare genetic diseases with evolving phenotypes. Inconsistencies between laboratories in classification of variant pathogenicity further cloud the use of the information in clinical practice. The development of guidelines for variant classification through a collaboration between ClinGen and the American Society of Hematology in genes associated with inherited thrombocytopenia and leukemia predisposition, including *ETV6*, is under way. Lastly, there are efforts in multiple laboratories worldwide to better understand the molecular mechanisms of abnormal platelet and leukocyte development as well as predisposition to malignancies resulting from *ETV6* dysfunction.

Acknowledgment

J.D.P. receives research funding from the National Heart, Lung and Blood Institute, National Institutes of Health (HL120728).

Authorship

Contribution: J.D.P. and C.C.P. wrote the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Jorge Di Paola, 12800 East 19th Ave, Mail Stop 8302, Aurora, CO 80045; e-mail: jorge.dipaola@ucdenver.edu; and Christopher C. Porter, 1760 Haygood Dr, E370, Atlanta, GA 30030; e-mail: chris.porter@emory.edu.

Footnotes

Submitted 24 January 2019; accepted 19 June 2019. Prepublished online as *Blood* First Edition paper, 27 June 2019; DOI 10.1182/blood.2019852418.

The online version of this article contains a data supplement.

REFERENCES

- Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
- Porter CC. Germ line mutations associated with leukemias. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):302-308.
- Zhang MY, Churpek JE, Keel SB, et al. Germline *ETV6* mutations in familial thrombocytopenia and hematologic malignancy. *Nat Genet*. 2015;47(2):180-185.
- Noetzli L, Lo RW, Lee-Sherick AB, et al. Germline mutations in *ETV6* are associated with thrombocytopenia, red cell macrocytosis and predisposition to lymphoblastic leukemia. *Nat Genet*. 2015;47(5):535-538.
- Poggi M, Canault M, Favier M, et al. Germline variants in *ETV6* underlie reduced platelet formation, platelet dysfunction and increased levels of circulating CD34+ progenitors. *Haematologica*. 2017;102(2):282-294.
- Melazzini F, Palombo F, Balduini A, et al. Clinical and pathogenic features of *ETV6*-related thrombocytopenia with predisposition to acute lymphoblastic leukemia. *Haematologica*. 2016;101(11):1333-1342.
- Topka S, Vijai J, Walsh MF, et al. Germline *ETV6* mutations confer susceptibility to acute lymphoblastic leukemia and thrombocytopenia. *PLoS Genet*. 2015;11(6):e1005262.
- Dirse V, Norvilas R, Gineikiene E, Matuzeviciene R, Griskevicius L, Preiksaitiene E. *ETV6* and *NOTCH1* germline variants in adult acute leukemia. *Leuk Lymphoma*. 2018;59(4):1022-1024.
- Duployez N, Abou Chahla W, Lejeune S, et al. Detection of a new heterozygous germline *ETV6* mutation in a case with hyperdiploid acute lymphoblastic leukemia. *Eur J Haematol*. 2018;100(1):104-107.
- Moriyama T, Metzger ML, Wu G, et al. Germline genetic variation in *ETV6* and risk of childhood acute lymphoblastic leukaemia: a systematic genetic study. *Lancet Oncol*. 2015;16(16):1659-1666.
- Rampersaud E, Ziegler DS, Iacobucci I, et al. Germline deletion of *ETV6* in familial acute lymphoblastic leukemia. *Blood Adv*. 2019;3(7):1039-1046.
- Churchman ML, Qian M, Te Kronnie G, et al. Germline genetic *IKZF1* variation and predisposition to childhood acute lymphoblastic leukemia. *Cancer Cell*. 2018;33(5):937-948.e8.
- Wang M, Gu D, Du M, et al. Common genetic variation in *ETV6* is associated with colorectal cancer susceptibility. *Nat Commun*. 2016;7:11478.
- Bohlander SK. *ETV6*: a versatile player in leukemogenesis. *Semin Cancer Biol*. 2005;15(3):162-174.
- Chakrabarti SR, Nucifora G. The leukemia-associated gene *TEL* encodes a transcription repressor which associates with *SMRT* and *mSin3A*. *Biochem Biophys Res Commun*. 1999;264(3):871-877.
- Wang L, Hiebert SW. *TEL* contacts multiple co-repressors and specifically associates with histone deacetylase-3. *Oncogene*. 2001;20(28):3716-3725.
- Poirel H, Oury C, Carron C, et al. The *TEL* gene products: nuclear phosphoproteins with DNA binding properties. *Oncogene*. 1997;14(3):349-357.
- Hanson CA, Wood LD, Hiebert SW. Cellular stress triggers *TEL* nuclear export via two genetically separable pathways. *J Cell Biochem*. 2008;104(2):488-498.
- Arai H, Maki K, Waga K, et al. Functional regulation of *TEL* by p38-induced phosphorylation. *Biochem Biophys Res Commun*. 2002;299(1):116-125.
- Lopez RG, Carron C, Oury C, Gardellin P, Bernard O, Ghysdael J. *TEL* is a sequence-specific transcriptional repressor. *J Biol Chem*. 1999;274(42):30132-30138.
- Hock H, Shimamura A. *ETV6* in hematopoiesis and leukemia predisposition. *Semin Hematol*. 2017;54(2):98-104.
- Wang LC, Kuo F, Fujiwara Y, Gilliland DG, Golub TR, Orkin SH. Yolk sac angiogenic defect and intra-embryonic apoptosis in mice lacking the *Ets*-related factor *TEL*. *EMBO J*. 1997;16(14):4374-4383.
- Hock H, Meade E, Medeiros S, et al. *Tel/Etv6* is an essential and selective regulator of adult hematopoietic stem cell survival. *Genes Dev*. 2004;18(19):2336-2341.
- Wang LC, Swat W, Fujiwara Y, et al. The *TEL/ETV6* gene is required specifically for hematopoiesis in the bone marrow. *Genes Dev*. 1998;12(15):2392-2402.
- Boily G, Larose J, Langlois S, Sinnott D. Identification of transcripts modulated by *ETV6* expression. *Br J Haematol*. 2007;136(1):48-62.
- Fears S, Gavin M, Zhang DE, et al. Functional characterization of *ETV6* and *ETV6/CBFA2* in the regulation of the *MCSFR* proximal promoter. *Proc Natl Acad Sci USA*. 1997;94(5):1949-1954.
- Fenrick R, Wang L, Nip J, et al. *TEL*, a putative tumor suppressor, modulates cell growth and cell morphology of *ras*-transformed cells while repressing the transcription of *stromelysin-1*. *Mol Cell Biol*. 2000;20(16):5828-5839.
- Kwiatkowski BA, Zielinska-Kwiatkowska AG, Bauer TR Jr, Hickstein DD. The *ETS* family member *Tel* antagonizes the *Fli-1* phenotype in hematopoietic cells. *Blood Cells Mol Dis*. 2000;26(1):84-90.
- Kwiatkowski BA, Bastian LS, Bauer TR Jr, Tsai S, Zielinska-Kwiatkowska AG, Hickstein DD. The *ets* family member *Tel* binds to the *Fli-1* oncoprotein and inhibits its transcriptional activity. *J Biol Chem*. 1998;273(28):17525-17530.

30. Hunger SP, Mullighan CG. Redefining ALL classification: toward detecting high-risk ALL and implementing precision medicine. *Blood*. 2015;125(26):3977-3987.
31. Rompaey LV, Potter M, Adams C, Grosveld G. Tel induces a G1 arrest and suppresses Ras-induced transformation. *Oncogene*. 2000;19(46):5244-5250.
32. Gunji H, Waga K, Nakamura F, et al. TEL/AML1 shows dominant-negative effects over TEL as well as AML1. *Biochem Biophys Res Commun*. 2004;322(2):623-630.
33. Raynaud S, Cave H, Baens M, et al. The 12;21 translocation involving TEL and deletion of the other TEL allele: two frequently associated alterations found in childhood acute lymphoblastic leukemia. *Blood*. 1996;87(7):2891-2899.
34. Zuna J, Ford AM, Peham M, et al. TEL deletion analysis supports a novel view of relapse in childhood acute lymphoblastic leukemia. *Clin Cancer Res*. 2004;10(16):5355-5360.
35. Mullighan CG, Miller CB, Radtke I, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. *Nature*. 2008;453(7191):110-114.
36. Holmfeldt L, Wei L, Diaz-Flores E, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. *Nat Genet*. 2013;45(3):242-252.
37. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med*. 2014;371(11):1005-1015.
38. Harvey RC, Mullighan CG, Wang X, et al. Identification of novel cluster groups in pediatric high-risk B-precursor acute lymphoblastic leukemia with gene expression profiling: correlation with genome-wide DNA copy number alterations, clinical characteristics, and outcome. *Blood*. 2010;116(23):4874-4884.
39. Van Vlierberghe P, Ambesi-Impiombato A, Perez-Garcia A, et al. ETV6 mutations in early immature human T cell leukemias. *J Exp Med*. 2011;208(13):2571-2579.
40. Zhang J, Ding L, Holmfeldt L, et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. *Nature*. 2012;481(7380):157-163.
41. Barjesteh van Waalwijk van Doorn-Khosrovani S, Spensberger D, de Knecht Y, Tang M, Löwenberg B, Delwel R. Somatic heterozygous mutations in ETV6 (TEL) and frequent absence of ETV6 protein in acute myeloid leukemia. *Oncogene*. 2005;24(25):4129-4137.
42. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209-2221.
43. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med*. 2011;364(26):2496-2506.
44. Paulsson K, Forestier E, Lilljebjörn H, et al. Genetic landscape of high hyperdiploid childhood acute lymphoblastic leukemia. *Proc Natl Acad Sci USA*. 2010;107(50):21719-21724.
45. Godley LA, Shimamura A. Genetic predisposition to hematologic malignancies: management and surveillance. *Blood*. 2017;130(4):424-432.
46. Drazer MW, Feurstein S, West AH, Jones MF, Churpek JE, Godley LA; University of Chicago Hematopoietic Malignancies Cancer Risk Team. How I diagnose and manage individuals at risk for inherited myeloid malignancies. *Blood*. 2016;128(14):1800-1813.
47. Dupuis A, Gachet C. Inherited platelet disorders: management of the bleeding risk. *Transfus Clin Biol*. 2018;25(3):228-235.
48. Porter CC, Druley TE, Erez A, et al. Recommendations for surveillance for children with leukemia-predisposing conditions. *Clin Cancer Res*. 2017;23(11):e14-e22.
49. Druker H, Zellek K, McGee RB, et al. Genetic counselor recommendations for cancer predisposition evaluation and surveillance in the pediatric oncology patient. *Clin Cancer Res*. 2017;23(13):e91-e97.
50. Xiao H, Shi J, Luo Y, et al. First report of multiple CEBPA mutations contributing to donor origin of leukemia relapse after allogeneic hematopoietic stem cell transplantation. *Blood*. 2011;117(19):5257-5260.
51. Berger G, van den Berg E, Sikkema-Raddatz B, et al. Re-emergence of acute myeloid leukemia in donor cells following allogeneic transplantation in a family with a germline DDX41 mutation. *Leukemia*. 2017;31(2):520-522.