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Familial predisposition of myeloid malignancies: Biological and clinical significances of recurrent germline mutations

Germline *ETV6* mutations and predisposition to hematological malignancies

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Abstract Patients with thrombocytopenia 5 have an autosomal dominant disorder of decreased platelet number with tendency to bleed, usually presenting in childhood, and have been found to have germline mutations in *ETV6*, which encodes a master hematopoietic transcription factor. Some patients who present similarly have inherited mutations in *RUNX1* or *ANKRD26*. All three germline syndromes are also associated with a predisposition to myelodysplastic syndrome (MDS) and acute leukemia (AL). Since the first description of germline *ETV6* mutations, 18 families have been reported. The common phenotype is mild to moderate thrombocytopenia with a variable predisposition to acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and MDS. This review will focus upon the role of *ETV6* in hematopoiesis, especially in myeloid differentiation and maturation, and will describe the functional effects of mutant ETV6. The review will also provide an overview of common clinical features as well as recommendations for patient screening and follow-up and will debate whether additional clinical features should be included with the germline *ETV6* syndrome.

Keywords ETV6 · Germline · Predisposition · Thrombocytopenia · Acute leukemia

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Introduction

ETV6-gene function and its importance in hematopoiesis

ETV6, located at chromosome 12p13, has been known to be an important player in hematopoiesis since its first description as a translocation partner of *PDGFB* in chronic myelomonocytic leukemia in 1994 [1]. Since then, more than 30 *ETV6* translocation partners have been reported within acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), myeloproliferative neoplasms, and T cell lymphoma, thus making *ETV6* one of the most commonly rearranged genes in human acute leukemia (AL) and MDS [2]. The fusion of *ETV6* and *RUNX1* occurs in 22% of children with ALL, and is thereby the most common cytogenetic subgroup in childhood ALL [3]. Somatic mutations in *ETV6* have been described in a variety of hematologic malignancies, among those children with T-ALL [3], and patients with MDS [4–6], AML [7], B-ALL, chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML) and mixed-phenotype acute leukemia [8]. Mutation frequencies in MDS range from 1 to 3% [4–6], with some evidence that mutations in *ETV6* are associated with a poor overall survival [5]. Likewise, somatic *ETV6* mutations in AML are rare but recurrent events [7, 9]. Deletions involving the cytogenetic region 12p13 are common in hematopoietic malignancies of both lymphoid and myeloid origin, notably in MDS with monosomy 7 [10] and AML with complex karyotypes [11–14].

ETV6 encodes a master hematopoietic transcription factor (TF) that is part of a large family, comprising 28 members in humans, all of which encode proteins with a

DNA-binding domain designated the ETS domain, which binds the same DNA consensus sequence. *ETV6* comprises eight exons and encodes a TF with three functional domains: a highly conserved N-terminal PNT domain which mediates homo- and heterodimerization and is required for nuclear localization of the protein, a central regulatory domain, and a C-terminal ETS domain (Fig. 1a).

ETV6 specifically acts as a transcriptional repressor that requires homodimerization to exert repression [15–19]. The DNA-binding capacity of ETV6 is also strongly regulated by an auto-inhibitory mechanism [19]. ETV6 inhibits the activity of other ETS domain containing TFs by heterodimerization, such as FLI1 [20]. FLI1 is critical for the megakaryocyte lineage commitment where it acts in tandem with GABPA [21].

Etv6 knockout mice are embryonically lethal [22], and *Etv6* knockdown in zebrafish causes defects in primitive hematopoiesis [23]. Hematopoietic progenitor cells in conditional *Etv6* knockout mice fail to colonize the bone marrow, pointing to an important role for Etv6 in the regulation of early hematopoiesis in the bone marrow [24]. However, Etv6 is not essential for the maintenance of mature lineages after commitment of the hematopoietic stem cells, except for a terminal defect in megakaryocyte maturation shown by peripheral thrombocytopenia and an increase in megakaryocyte colony-forming cells [25].

ETV6 in myeloid differentiation and maturation

ETV6 plays a distinct role in myeloid differentiation. Yamagata et al. found that *ETV6* overexpression in murine myeloid 32Dcl cells, which can terminally differentiate into neutrophils, leads to growth restriction and apoptosis, demonstrating that ETV6 exerts tumor-suppressive functions [26]. *Etv6* knockout mice display moderately reduced neutrophil counts [25]. Further experiments using transgenic mice and ES cells expressing human *ETV6* indicated that ETV6 enhances the proliferation of erythrocyte/megakaryocyte common progenitors and accelerates terminal erythroid differentiation via stimulation of hemoglobin

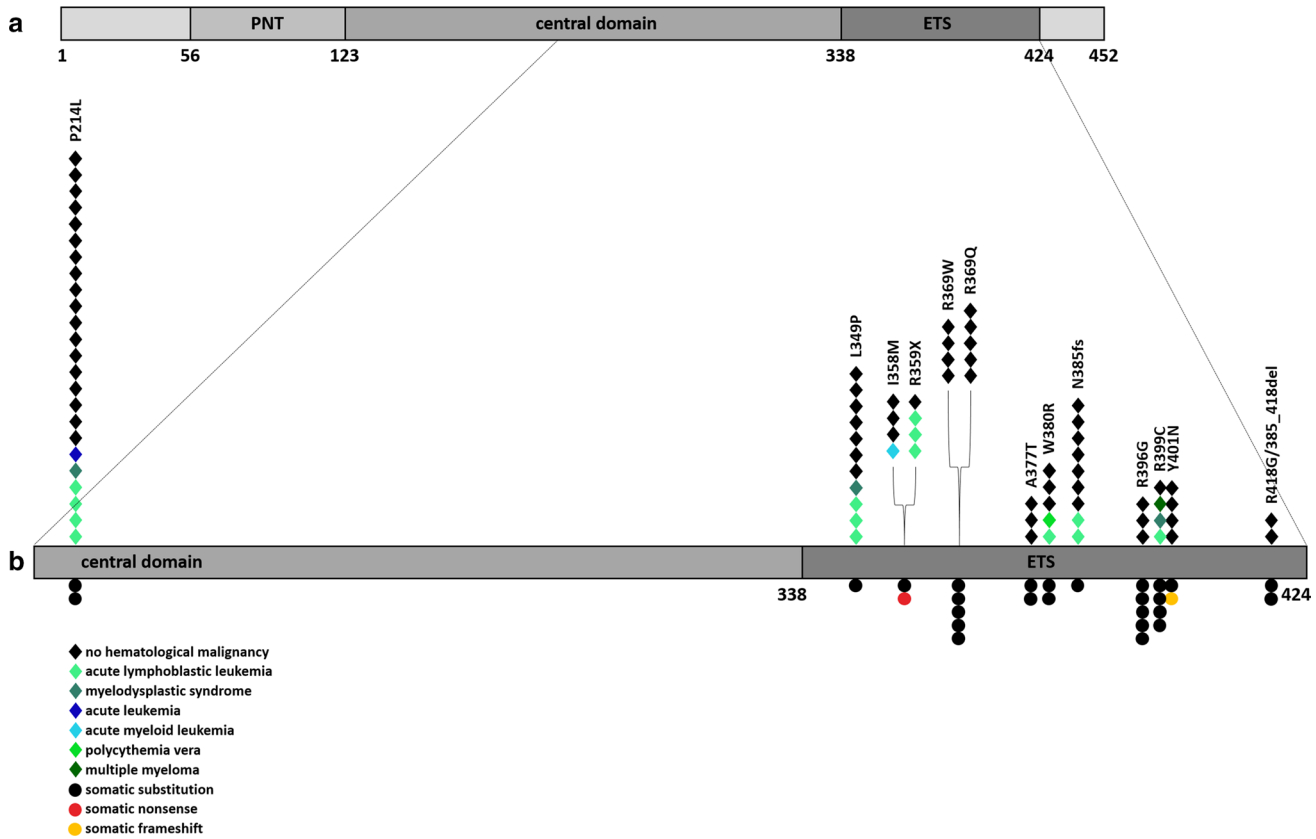

Fig. 1 Schematic diagram of ETV6, including the different functional domains and the distribution of germline and somatic mutations. **a** ETV6 with its three functional domains, the N-terminal PNT domain, the central domain, and the C-terminal DNA-binding ETS domain. **b** Overview of all reported germline ETV6 amino acid changes spanning both the central and ETS domain. *Each diamond* represents one patient, and the phenotype (various hematological malignancies) is depicted using *different colors*. Only confirmed carriers are shown. *Each circle* represents a somatic mutation affecting this specific amino acid residue, using data for both hematological and solid neoplasms presented in the COSMIC database (cancer.sanger.ac.uk)

synthesis [27]. Likewise, by introducing human wild-type *ETV6* into mouse erythroleukemia cells and subsequent overexpression, ETV6 stimulated erythroid differentiation [28]. A more recent study on *Etv6* function in zebrafish showed that *Etv6* knockdown reduced the levels of progenitor cells, myeloid cells, and erythrocytes and impaired the differentiation of zebrafish heterophils, the piscine neutrophil equivalent [23]. These studies indicate a broad function of ETV6 in early embryonic and adult hematopoiesis as well as in erythroid and megakaryocytic differentiation and maturation.

ETV6 mutations as a germline syndrome

Common clinical features of ETV6 germline syndromes

An example of a pedigree with germline *ETV6* mutation is shown in Fig. 2. The striking feature in these families is the segregating thrombocytopenia and the predisposition to hematological malignancies, with ALL being the most frequent. As shown in the pedigree, the most common presenting sign of patients with germline *ETV6* mutations is a mild to moderate thrombocytopenia, with platelet counts typically ranging from 32 to 118 G/L (Table 1). Some patients exhibit a bleeding tendency, which is usually mild to moderate, with very few severe bleeding episodes. However, Moriyama et al. described a family with a nonsense mutation in the ETS domain with four carriers, but only two of them being mildly thrombocytopenic [29]. The majority of patients have platelets of normal size. However, the mean platelet volume (MPV) is variable (Table 1). A normal or slightly increased platelet size has also been described for the two other germline syndromes with thrombocytopenia and predisposition to leukemia caused by mutations in *RUNX1* and *ANKRD26* [30, 31]. The association of germline *ETV6* mutation with macrocytosis is inconsistent, and most individuals show a mean corpuscular volume within the normal range (Table 1).

To date, fewer than 20 families have been described, which makes it impossible to speculate about founder mutations. Review of the current literature reveals that some families were of German [32], European [29, 33, 34], Polish/Moroccan [34], Scottish [32], and Native American [32, 34] ancestry.

In general, *ETV6* germline mutations predispose to both lymphoid and myeloid hematological malignancies. Predisposition to ALL is more frequent, especially to childhood B-ALL (Table 1). The ratio of lymphoid versus myeloid malignancies is roughly 2:1. Myeloid malignancies encompass MDS and AML, which seem to occur at a younger age than usual. One case of *JAK2* V617F-positive polycythemia vera in a carrier has been reported [35]. Another patient has been diagnosed with multiple myeloma at the age of 51 years. However, the multiple

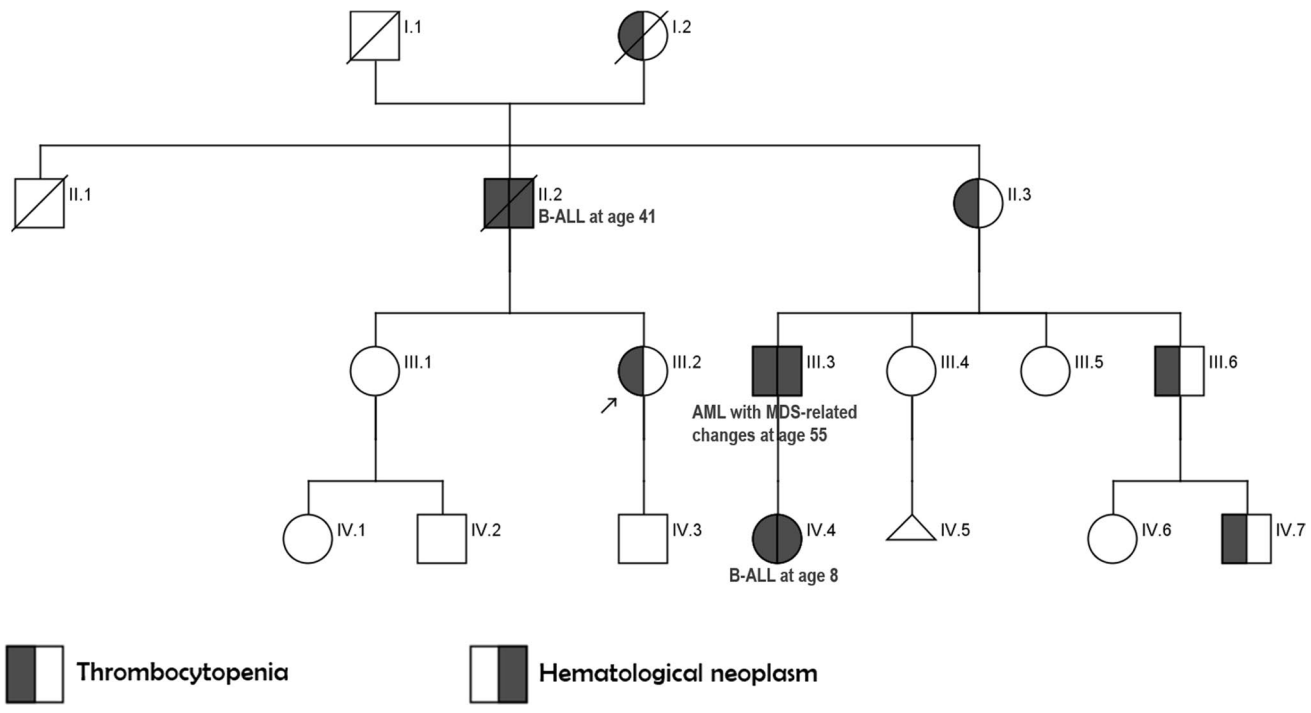

Fig. 2 An example of a pedigree highly suspicious for germline *ETV6* mutations. The phenotype is defined by thrombocytopenia and a predisposition to hematological malignancies segregating over four generation

Table 1 Clinical parameters seen in families with germline *ETV6* mutations

Publication	*ETV6* mutation	No of carriers	Average platelet count G/l	Average MPV (fl)	Average MCV (fl)	Hematological malignancies	Age at diagnosis of hem malignancy	Non-hematological disease	Non-hematological malignancy
[35]	P214L	6	80	9.4	90	Common ALL, B-ALL	7, 15	None	Breast fibroadenoma and meningioma (1)
	R369W	4	105	8.8	91	None		None	None
	W380R	5	82	8.1	94	PV, common ALL	37, 7	None	None
	N385Vfs	5	87	8.3	99	Common ALL	3	None	Breast cancer (1), breast fibroadenoma (1)
[29]	R359X	4	162	7.8	92	ALL, ALL, ALL	9, 3, 2	Learning disability (1), mild intellectual disability (1)	None
[33]	P214L	5	90	10.6	96	B cell ALL, B cell ALL	3, 37	None	None
	P214L	3	75	10.2	92	ALL	14	None	None
	R418G/385_418del	2	100	n.a.	96	None		None	None
[34]	L349P	11	32	n.a.	83	ALL, ALL, ALL, MDS/ALL	n.a.	Arthritis (1), ankylosing spondylitis/uveitis (1), cleft lip/palate (1)	Renal cell carcinoma (1), duodenal adenocarcinoma (1)
	N385Vfs	4	n.a.	n.a.	n.a.	ALL, secondary MDS/AML	n.a.	Craniofacial/skeletal dysmorphisms (1)	None
[38]	P214L	9	62	9.1	92	MDS	70	None	None
	A377T	3	85	8.6	93	None		None	None
	Y401N	4	99	9.7	90	None		None	None
	I358M	4	85	10.7	94	AML	8	None	None
	R396G	3	70	10.6	n.a.	None		None	None
[32]	R399C	4	86	7.5	93	MDS, pre B cell ALL, (t?)-MM	17, 7, 51	Myopathy (2), gastrointestinal dysmotility (1), GERD (1), developmental delay (1), seizures (1), dental disease (l), delayed puberty (1)	Colorectal carcinoma (1)
	R369Q	5	118	7.9	95	None		Reading disability (3), GERD (4), esophageal stricture (2)	Skin cancer (4), colon cancer (1)
	P214L	1	42	8.4	90	T-cell/myeloid mixed-phenotype acute leukemia	50	None	None

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *GERD* gastroesophageal reflux disease, *MDS* myelodysplastic syndrome, *MM* multiple myeloma, *n.a.* not assessed, *PV* polycythemia vera

myeloma could potentially be therapy related, since the patient had received chemotherapy for colorectal cancer 6 years earlier [32]. The penetrance of hematological malignacies varies strongly both between the different affected amino acid residues as well as between families affected by the same *ETV6* mutation. (Fig. 1b; Table 1). In six families, no hematological malignancy has been described so far. However, the carriers display the common mild to moderate thrombocytopenia seen in almost all germline *ETV6* carriers. Also, in the nine patients with germline mutations affecting the amino acid residue 369, no hematological malignancies have been described to date (Fig. 1b; Table 1). Overall, approximately 30% of all carriers have been diagnosed with some kind of hematologic malignancy.

Other non-hematological malignancies in carriers have been documented. These malignancies include colorectal carcinoma, duodenal adenocarcinoma, breast cancer, breast fibroadenoma, meningioma, renal cell cancer, and skin cancers [32, 34, 35] (Table 1). Due to the very limited number of families reported so far, it is difficult to assess whether there is a pattern of solid cancers associated with the germline syndrome. There is evidence for one common germline variant in intron 4 of *ETV6*, rs2238126, which seems to be associated with susceptibility to colorectal carcinoma. The rs2238126 A allele might preferentially bind MAX, a transcriptional enhancer, which then dimerizes with MYC and induces cell cycle progression [36].

There are also several other distinctive clinical features that may or may not be associated with germline *ETV6* mutations. For instance, one family with a cluster of autoimmune disorders, including arthritis and ankylosing spondylitis, has been described [34]. Two other families display a cluster of gastroesophageal reflux and esophageal stricture, and in one of those families, several cases of myopathy have been described [32]. However, more families must be studied to determine whether some of these features are part of the phenotype.

Germline *ETV6* mutations might be more common than previously recognized. Targeted sequencing of DNA from bone marrow or peripheral blood of 4405 childhood ALL patients identified 31 exonic variants in 35 patients, which represents ~1% of the childhood ALL cohort. Information about family history or personal history of cytopenias was not available. These variants were classified as deleterious according to their minor allele frequency in the population and *in silico* analyses of their effect on the protein structure. However, no functional analyses were performed. Interestingly, children with germline variants in *ETV6* were significantly older, and hyperdiploid leukemia as a cytogenetic subgroup was significantly overrepresented [29].

Functional analyses of ETV6 mutants

ETV6 is an important transcriptional repressor that acts in the cell nucleus and requires dimerization and oligomerization. Interestingly, among the *ETV6* mutations tested to date, all affect the nuclear localization of the protein to some degree, often causing aberrant cytoplasmic localization. This mislocalization of the protein implies a dominant-negative effect of mutant over wild-type ETV6 via oligomerization, a phenomenon previously reported in patients with somatic mutations [7, 28, 37]. An impaired nuclear localization has been shown for the P214L [32, 33], R369Q, and R399C mutants [32], for R418G [33] as well as for the mutants L349P and R385fs [34]. *MMP3* and *PF4*, which harbor multiple ETS binding sites, are usually transcriptionally repressed by ETV6. The repressive ability was significantly reduced in the ETV6 P214L, R369Q, R399C, L349P and N385fs mutants [32, 34]. The same has been shown for repression of the known ETV6 target *stromelysin-1*, with less transcriptional repression when expressing the mutants P214L, R418G, and 385_418del [33]. The reciprocal experiment of analyzing the expression of target genes like *EGR1* and *TRAF1* that are known to be upregulated by ETV6 showed minimal or no upregulation of these genes in the P214L, R369Q, R399C, L349P, and N385fs mutants [34]. ETV6 interacts with several corepressors like SMRT, mSin3A, and N-CoR. For both A377T and Y401N, impaired interaction with these corepressors has been reported, which affects recruitment of the corepressors [38].

No particular defects in platelet aggregation, activation, or changes of the major glycoproteins of the platelet surface have been detected. However, the platelets of carriers show an impaired ability to spread on fibrinogen [35]. Furthermore, patient-derived megakaryocytes reveal a defect in megakaryocytic maturation and formation of proplatelets both in terms of morphological and quantitative findings, demonstrated for P214L [33, 38], Y401N [38], and R418G [33].

Germline ETV6 hot spot mutations

A germline hot spot mutation in ETV6 is P214L, with five families described so far. Interestingly, compared to the other germline variants, this mutation does not affect the ETS domain, but is located instead in a serine–proline phosphorylation motif present in the central regulatory domain and represses DNA binding by the ETS domain by approximately tenfold [19] and interacts with the corepressors mSin3A and SMRT [16]. Carriers of the P214L show a defect in proplatelet formation and megakaryocytic maturation, altered proplatelet spreading, reduced transcript levels encoding several cytoskeletal proteins, and modification of ETV6 subcellular

localization [32–34, 38]. There are three other amino acid residues that are affected by germline mutations in two families—the frameshift mutation N385Vfs, Y401N, and mutations of residue 369 (R369W, R369Q). These mutations are all located within the ETS domain.

Most of the affected amino acid residues are known to be somatically mutated in both hematological malignancies and a broad spectrum of solid cancers (cancer.sanger.ac.uk) (Fig. 1b) [39].

Panel-based testing of acquired somatic mutations in hematologic malignancies of *ETV6* mutant patients revealed mutations in *BCOR, RUNX1*, and *KRAS* [32], and a gene fusion between *PAX5* and *SHB* in a patient with ALL [33]. These mutations might be additional driver mutations finally leading to overt development of hematological malignancies in these patients. Germline mutations in both *PAX5* and *RUNX1* are known as leukemia predisposition syndromes [30, 40].

Patient screening and clinical follow-up

Any family with a pattern of familial thrombocytopenia and a predisposition to hematological malignancies, especially ALL, AML, and MDS, should be screened for germline *ETV6* mutations. The gold standard for germline testing is DNA derived from cultured skin fibroblasts. However, if skin fibroblasts are not available, other tissue such as cultured bone marrow-derived stromal cells may be used, depending on the laboratory. Also, if DNA can be obtained from multiple family members, they can be screened for segregating mutations. Once there is evidence for a pathogenic *ETV6* germline mutation, patients should undergo periodic follow-up with complete blood counts, white blood cell differentials, a clinical examination, as well as a bone marrow biopsy at baseline and at the time of any significant, persistent change in peripheral blood counts. Patients should also be educated regarding possible excessive bleeding with surgery, childbirth, and injury due to underlying thrombocytopenia. A careful clinical examination and regular cancer screening are recommended considering the cluster of non-hematological neoplasms (e.g., colon cancer) seen in some families. Genetic counseling and site-specific testing should be offered to any at-risk family member. Matched-related stem cell donors should be considered very carefully, and donors with known germline mutation or unclear carrier status should be avoided [41, 42].

Conclusion

Germline *ETV6* mutations are emerging as an important cause of inherited thrombocytopenias, accompanied by a risk for the development of acute leukemias, more often lymphoid, but also myeloid, and other hematopoietic and potentially solid tumors as well. The increased awareness of germline susceptibility syndromes will likely result in the identification of additional families, which will help define the clinical spectrum of abnormalities seen in these individuals. Other inherited gene mutations yet to be discovered may result in syndrome phenocopies, as germline *RUNX1* and *ANKRD26* mutations are already recognized as presenting with similar signs and symptoms. We recommend a high index of suspicion for these syndromes, with use of professional genetic counselors and appropriate clinical testing and long-term surveillance of germline mutation carriers.

Compliance with ethical standards

Conflict of interest Lucy A. Godley receives royalties from her coauthored article on inherited hematopoietic malignancies in UpToDate. Dr. Feurstein declares no competing financial interests.

References

1. Golub TR, Barker GF, Lovett M, Gilliland DG. Fusion of PDGF receptor beta to a novel ets-like gene, tel, in chronic myelomonocytic leukemia with t(5;12) chromosomal translocation. Cell. 1994;77:307–16.
2. De Braekeleer E, Douet-Guilbert N, Morel F, Le Bris M-J, Basinko A, De Braekeleer M. ETV6 fusion genes in hematological malignancies: a review. Leuk Res. 2012;36:945–61.
3. Mullighan CG. The molecular genetic makeup of acute lymphoblastic leukemia. Hematol Am Soc Hematol Educ Program. 2012;2012:389–96.
4. Bejar R, Stevenson KE, Caughey BA, Abdel-Wahab O, Steensma DP, Galili N, et al. Validation of a prognostic model and the impact of mutations in patients with lower-risk myelodysplastic syndromes. J Clin Oncol. 2012;30:3376–82.
5. Bejar R, Stevenson K, Abdel-Wahab O, Galili N, Nilsson B, Garcia-Manero G, et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med. 2011;364:2496–506.
6. Walter MJ, Shen D, Shao J, Ding L, White BS, Kandoth C, et al. Clonal diversity of recurrently mutated genes in myelodysplastic syndromes. Leukemia. 2013;27:1275–82.
7. Barjesteh van Waalwijk van Doorn-Khosrovani S, Spensberger D, de Knegt 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;24:4129–37.
8. Wang Q, Dong S, Yao H, Wen L, Qiu H, Qin L, et al. ETV6 mutation in a cohort of 970 patients with hematologic malignancies. Haematologica. 2014;99:e176–8.
9. Silva FPG, Morolli B, Storlazzi CT, Zagaria A, Impera L, Klein B, et al. ETV6 mutations and loss in AML-M0. Leukemia. 2008;22:1639–43.
10. Wall M, Rayeroux KC, MacKinnon RN, Zordan A, Campbell LJ. ETV6 deletion is a common additional abnormality in patients

with myelodysplastic syndromes or acute myeloid leukemia and monosomy 7. Haematologica. 2012;97:1933–6.
11. Byrd JC, Mrózek K, Dodge RK, Carroll AJ, Edwards CG, Arthur DC, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). Blood. 2002;100:4325–36.
12. Feurstein S, Rücker FG, Bullinger L, Hofmann W, Manukjan G, Göhring G, et al. Haploinsufficiency of ETV6 and CDKN1B in patients with acute myeloid leukemia and complex karyotype. BMC Genom. 2014;15:784.
13. Kayser S, Zucknick M, Döhner K, Krauter J, Köhne C-H, Horst HA, et al. Monosomal karyotype in adult acute myeloid leukemia: prognostic impact and outcome after different treatment strategies. Blood. 2012;119:551–8.
14. Rücker FG, Bullinger L, Schwaenen C, Lipka DB, Wessendorf S, Fröhling S, et al. Disclosure of candidate genes in acute myeloid leukemia with complex karyotypes using microarray-based molecular characterization. J Clin Oncol. 2006;24:3887–94.
15. Kim CA. Polymerization of the SAM domain of TEL in leukemogenesis and transcriptional repression. EMBO J. 2001;20:4173–82.
16. Chakrabarti SR, Nucifora G. The leukemia-associated gene TEL encodes a transcription repressor which associates with SMRT and mSin3A. Biochem Biophys Res Commun. 1999;264:871–7.
17. Potter MD, Buijs A, Kreider B, van Rompaey L, Grosveld GC. Identification and characterization of a new human ETS-family transcription factor, TEL2, that is expressed in hematopoietic tissues and can associate with TEL1/ETV6. Blood. 2000;95:3341–8.
18. Lopez RG, Carron C, Oury C, Gardellin P, Bernard O, Ghysdael J. TEL is a sequence-specific transcriptional repressor. J Biol Chem. 1999;274:30132–8.
19. Green SM, Coyne HJ, McIntosh LP, Graves BJ. DNA binding by the ETS protein TEL (ETV6) is regulated by autoinhibition and self-association. J Biol Chem. 2010;285:18496–504.
20. Kwiatkowski BA, Bastian LS, Bauer TR, 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;273:17525–30.
21. Tijssen MR, Ghevaert C. Transcription factors in late megakaryopoiesis and related platelet disorders. J Thromb Haemost. 2013;11:593–604.
22. 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;16:4374–83.
23. Rasighaemi P, Onnebo SMN, Liongue C, Ward AC. ETV6 (TEL1) regulates embryonic hematopoiesis in zebrafish. Haematologica. 2015;100:23–31.
24. Wang LC, Swat W, Fujiwara Y, Davidson L, Visvader J, Kuo F, et al. The TEL/ETV6 gene is required specifically for hematopoiesis in the bone marrow. Genes Dev. 1998;12:2392–402.
25. Hock H. Tel/Etv6 is an essential and selective regulator of adult hematopoietic stem cell survival. Genes Dev. 2004;18:2336–41.
26. Yamagata T, Maki K, Waga K, Mitani K. TEL/ETV6 induces apoptosis in 32D cells through p53-dependent pathways. Biochem Biophys Res Commun. 2006;347:517–26.
27. Eguchi-Ishimae M, Eguchi M, Maki K, Porcher C, Shimizu R, Yamamoto M, et al. Leukemia-related transcription factor TEL/ETV6 expands erythroid precursors and stimulates hemoglobin synthesis. Cancer Sci. 2009;100:689–97.
28. Waga K, Nakamura Y, Maki K, Arai H, Yamagata T, Sasaki K, et al. Leukemia-related transcription factor TEL accelerates differentiation of Friend erythroleukemia cells. Oncogene. 2003;22:59–68.
29. Moriyama T, Metzger ML, Wu G, Nishii R, Qian M, Devidas M, et al. Germline genetic variation in ETV6 and risk of childhood acute lymphoblastic leukaemia: a systematic genetic study. Lancet Oncol. 2015;16:1659–66.
30. Song WJ, Sullivan MG, Legare RD, Hutchings S, Tan X, Kufrin D, et al. Haploinsufficiency of CBFA2 causes familial thrombocytopenia with propensity to develop acute myelogenous leukaemia. Nat Genet. 1999;23:166–75.
31. Pippucci T, Savoia A, Perrotta S, Pujol-Moix N, Noris P, Castegnaro G, et al. Mutations in the 5′ UTR of ANKRD26, the ankyrin repeat domain 26 gene, cause an autosomal-dominant form of inherited thrombocytopenia, THC2. Am J Hum Genet. 2011;88:115–20.
32. Zhang MY, Churpek JE, Keel SB, Walsh T, Lee MK, Loeb KR, et al. Germline ETV6 mutations in familial thrombocytopenia and hematologic malignancy. Nat Genet. 2015;47:180–5.
33. Noetzli L, Lo RW, Lee-Sherick AB, Callaghan M, Noris P, Savoia A, et al. Germline mutations in ETV6 are associated with thrombocytopenia, red cell macrocytosis and predisposition to lymphoblastic leukemia. Nat Genet. 2015;47:535–8.
34. Topka S, Vijai J, Walsh MF, Jacobs L, Maria A, Villano D, et al. Germline ETV6 mutations confer susceptibility to acute lymphoblastic leukemia and thrombocytopenia. PLoS Genet. 2015;11:e1005262.
35. Melazzini F, Palombo F, Balduini A, De Rocco D, Marconi C, Noris P, et al. Clinical and pathogenic features of ETV6-related thrombocytopenia with predisposition to acute lymphoblastic leukemia. Haematologica. 2016;101:1333–42.
36. Wang M, Gu D, Du M, Xu Z, Zhang S, Zhu L, et al. Common genetic variation in ETV6 is associated with colorectal cancer susceptibility. Nat Commun. 2016;7:11478.
37. Kawagoe H. TEL2, an ETS factor expressed in human leukemia, regulates monocytic differentiation of U937 cells and blocks the inhibitory effect of TEL1 on Ras-induced cellular transformation. Cancer Res. 2004;64:6091–100.
38. Poggi M, Canault M, Favier M, Turro E, Saultier P, Ghalloussi D, et al. Germline variants in ETV6 underlie reduced platelet formation, platelet dysfunction and increased levels of circulating CD34+ progenitors. Haematologica. 2017;102(2):282–94.
39. Forbes SA, Beare D, Gunasekaran P, Leung K, Bindal N, Boutselakis H, et al. COSMIC: exploring the world's knowledge of somatic mutations in human cancer. Nucleic Acids Res. 2015;43:D805–11.
40. Shah S, Schrader KA, Waanders E, Timms AE, Vijai J, Miething C, et al. A recurrent germline PAX5 mutation confers susceptibility to pre-B cell acute lymphoblastic leukemia. Nat Genet. 2013;45:1226–31.
41. Feurstein S, Drazer MW, Godley LA. Genetic predisposition to leukemia and other hematologic malignancies. Semin Oncol. 2016;43:598–608.
42. Churpek JE, Godley LA. How I diagnose and manage individuals at risk for inherited myeloid malignancies. Blood. 2016;128:1800–13.