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ETV6 Thrombocytopenia and Predisposition to Leukemia

Synonyms: *ETV6*-Linked Leukemia / Familial Thrombocytopenia Syndrome, Thrombocytopenia 5 (THC5)

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Summary

Clinical characteristics

Individuals with *ETV6* thrombocytopenia and predisposition to leukemia most often present with a lifelong history of thrombocytopenia, which is usually in the mild to moderate range. No syndromic features or associations are consistently shared across pedigrees. Affected individuals also have a moderate risk of developing a hematologic malignancy (with B-cell acute lymphoblastic leukemia [B-ALL] being the most common) and possibly other malignant solid tumors, particularly colorectal cancer.

Diagnosis/testing

The diagnosis of *ETV6* thrombocytopenia and predisposition to leukemia is established in a proband by identification of a heterozygous germline pathogenic variant in *ETV6* by molecular genetic testing.

Management

Treatment of manifestations: For clinical bleeding, local measures with consideration of antifibrinolytic agents, desmopressin, and/or platelet transfusion if bleeding is moderate to severe. For neoplasm, standard neoplasm-specific therapy with consideration of indications for stem cell transplantation, eligibility, and available donors.

Prevention of secondary complications: For individuals with a history of moderate or severe bleeding, antifibrinolytic agents or desmopressin may be considered prior to surgical procedures to reduce bleeding

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complications. Platelet transfusions should be used judiciously, particularly in women of childbearing age, to reduce the risk of alloimmunization.

Surveillance: Complete blood count with differential every six to 12 months and consideration of bone marrow aspirate and biopsy annually. The frequency of such screening must be weighed against the burden of the screening protocol, particularly in young children. The exact frequency of CBC and bone marrow evaluations should be determined on a case-by-case basis by the physician and in consideration of patient/family preferences.

Agents/circumstances to avoid: For those with a history of bleeding, avoidance of medications that decrease platelet function (e.g., aspirin, nonsteroidal anti-inflammatories) and avoidance of participation in contact sports are recommended.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of clinical surveillance for malignancy and management of potential significant thrombocytopenia.

Pregnancy management: Platelet counts should be monitored during pregnancy and prior to delivery. Platelet transfusions prior to invasive procedures (e.g., epidural analgesia or cæsarean section) or at the time of delivery may be considered in those with a history of bleeding or severe thrombocytopenia, on a case-by-case basis.

Genetic counseling

ETV6 thrombocytopenia and predisposition to leukemia is inherited in an autosomal dominant manner. To date, all affected individuals have inherited the *ETV6* pathogenic variant from a parent, although in some instances the heterozygous parent did have any known clinical findings. The offspring of an individual with *ETV6* thrombocytopenia and predisposition to leukemia are at 50% risk of inheriting the *ETV6* pathogenic variant. Once the *ETV6* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

ETV6 thrombocytopenia and predisposition to leukemia is a nonsyndromic genetic disorder of thrombocytopenia and high risk of leukemia without any other known congenital anomalies. Formal clinical diagnostic criteria have not been published.

Suggestive Findings

ETV6 thrombocytopenia and predisposition to leukemia should be considered in individuals with the following clinical and laboratory findings and family history.

Clinical findings

- Absent-to-moderate bleeding tendencies (e.g., menorrhagia, epistaxis, easy bruising, gum bleeding)
- Hematologic malignancies, including:
  - B-cell acute lymphoblastic leukemia (B-ALL), which is the most common
  - Acute myeloid leukemia (AML)
  - Myelodysplastic syndrome (MDS)
  - Myeloproliferative neoplasms (MPN)
  - Mixed phenotype acute leukemia (MPAL)
  - Multiple myeloma
- Possibly solid tumors, especially colorectal cancer

Laboratory findings

- Persistent and unexplained mild-to-moderate thrombocytopenia (platelet counts are often >75x10^9/L) with typically normal platelet size and occasionally accompanied by a high mean platelet volume
- Normal white blood cell count
- Normal hemoglobin concentration, sometimes with a high mean erythrocyte corpuscular volume (MCV)
- Abnormal bone marrow histology with small hyperchromatic megakaryocytes, disseminated toxic granulations, and dysplastic eosinophils in the absence of frank myelodysplasia

Family history

- One or more relatives with thrombocytopenia, acute leukemia, AND/OR solid tumors (particularly colorectal cancer) consistent with an autosomal dominant inheritance pattern
- Note: Absence of a known family history of thrombocytopenia, acute leukemia or solid tumors does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *ETV6* thrombocytopenia and predisposition to leukemia is established in a proband by identification of a heterozygous germline pathogenic variant in *ETV6* by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing and multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *ETV6* thrombocytopenia and predisposition to leukemia has not been considered may be diagnosed using genomic testing (see Option 2).

Option 1

When the clinical and laboratory findings suggest the diagnosis of *ETV6* thrombocytopenia and predisposition to leukemia, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ETV6* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

- **A multigene panel** that includes *ETV6* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. It is important to note that: (1) The genes included in panels and the diagnostic sensitivity of the testing for each gene vary by laboratory and are likely to change over time; (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview* and some panels may not include this gene; (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician; and (4) The methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the diagnosis of *ETV6* thrombocytopenia and predisposition to leukemia is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Note: A diagnosis of *ETV6* thrombocytopenia and predisposition to leukemia should not be confused with individuals who have malignancies with somatic chromosome rearrangements involving *ETV6* (see Genetically Related Disorders and Cancer and Benign Tumors).

Table 1. Molecular Genetic Testing Used in *ETV6*-Related Thrombocytopenia and Predisposition to Leukemia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ETV6	Sequence analysis [3]	23/26 [4]
	Gene-targeted deletion/duplication analysis [5]	2/26 [6, 7]
	Karyotype	1/26 [8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Di Paola & Porter [2019]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Paulsson et al [2010] reported one affected individual with an intragenic deletion involving exon 2.
7. Ross et al [2019] described a family in which individuals had a contiguous gene deletion that included *ETV6*. Rampersaud et al [2019] reported a germline 75-base-pair deletion of *ETV6* at the intron 6-exon 7 junction in all affected individuals. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Ross et al [2019]) may not be detected by these methods.
8. Järviaho et al [2019] described a pedigree in which two second-degree relatives developed B-ALL and were found to have a constitutional, balanced translocation involving *ETV6* (t(12;14)(p13.2;q23.1). An additional seven family members were found to harbor the same translocation but did not have a history of leukemia. No family members had thrombocytopenia.

Clinical Characteristics

Clinical Description

Individuals with *ETV6* thrombocytopenia and predisposition to leukemia most often present with a lifelong history of thrombocytopenia, which is usually in the mild to moderate range. No syndromic features or associations are consistently shared across pedigrees. Affected individuals also have a moderate risk of

developing a hematologic malignancy (with B-cell acute lymphoblastic leukemia [B-ALL] being the most common) and possibly other malignant solid tumors, particularly colorectal cancer.

To date, a total of 100 individuals from 26 families have been identified with a germline pathogenic variant in *ETV6* [Paulsson et al 2010, Di Paola & Porter 2019, Rampersaud et al 2019, Ross et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Thrombocytopenia

Thrombocytopenia is found in more than 90% of affected individuals at the time of diagnosis. However, most affected individuals have normal hemostasis or only a mild bleeding tendency.

Bleeding history

- Most affected individuals do not develop severe spontaneous bleeding episodes.
- Reported bleeding symptoms have included menorrhagia, epistaxis, easy bruising, and gum bleeding [Hock & Shimamura 2017].

Complete blood counts

- Most reported platelet counts are between 100-150x10^9/L.
- Some affected individuals have platelet counts as low as 32x10^9/L, but severe thrombocytopenia (<20 x 10^9/L) is rarely seen without concurrent myelodysplastic syndrome.
- Platelet size is usually normal by automated method (mean platelet volume) or microscopic analysis, although some affected individuals exhibit increased platelet volume.

Platelet structure and function studies. While abnormal platelet aggregation studies have been observed in a few individuals, no abnormal pattern on platelet membrane receptor distribution has been observed to date. Platelets have also shown abnormal clot retraction and spreading on fibrinogen surfaces [Poggi et al 2017, Di Paola & Porter 2019].

Bone Marrow Biopsy

Bone marrow aspirates in those without concurrent leukemias have revealed dyserythropoiesis, megakaryocyte hyperplasia, and small hypolobulated megakaryocytes [Di Paola & Porter 2019].

Lymphoid and Myeloid Malignancies

About 30% of individuals with *ETV6* thrombocytopenia and predisposition to leukemia develop a hematologic malignancy.

- Reported age range at time of diagnosis of a hematologic malignancy is between two and 82 years, with an average and median age of onset of 22 and 11 years, respectively [Di Paola & Porter 2019].
- About two thirds of affected individuals who develop a hematologic malignancy will have B-cell acute lymphoblastic leukemia.
- Other reported malignancies:
  - Other forms of acute lymphoblastic leukemia
  - Myelodysplastic syndrome (MDS)
  - Acute myeloid leukemia (AML)
  - Mixed phenotype acute leukemia
  - Diffuse large B-cell lymphoma
  - Polycythemia vera

Children with *ETV6* thrombocytopenia and predisposition to leukemia may be more likely to have hyperdiploid leukemia and be older at the time of diagnosis of leukemia than sporadic cases of leukemia [Moriyama et al

2015]. There is currently no evidence that the presence of a heterozygous germline *ETV6* pathogenic variant influences response to therapy, nor are there any recommendations to alter standard therapy based on the presence of a heterozygous germline *ETV6* pathogenic variant.

Solid Tumors

There may be an increased risk for the development of solid tumors in those with *ETV6* thrombocytopenia and predisposition to leukemia. While the exact risk has not been defined, at least seven molecularly confirmed individuals have a reported history of malignant solid tumors diagnosed before age 50 years, including two with colorectal cancer [Di Paola & Porter 2019].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

The penetrance of thrombocytopenia in this disorder is thought to exceed 90%.

The penetrance of malignancy, specifically lymphoid and myeloid, is estimated at 30%.

Prevalence

The prevalence of *ETV6* thrombocytopenia and predisposition to leukemia is unknown. To date, around 100 individuals have been reported to have this disorder.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ETV6*.

Sporadic tumors (including acute lymphoblastic leukemia) occurring as single tumors in the absence of any other findings of *ETV6* thrombocytopenia and predisposition to leukemia frequently harbor somatic variants in *ETV6* that are not present in the germline. In these circumstances predisposition to these tumors is not heritable. This most often includes a somatic translocation in childhood B-ALL, which results in a fusion protein ETV6-RUNX1.

For more information see Cancer and Benign Tumors.

Differential Diagnosis

Table 2. Genes of Interest in the Differential Diagnosis of *ETV6* Thrombocytopenia and Predisposition to Leukemia

Gene	Disorder [1]	Associated Malignancies	Hematologic Findings
ANKRD26	*ANKRD26* thrombocytopenia	MDS/AML AUL CLL CML	Thrombocytopenia
CYCS	Thrombocytopenia 4 (OMIM 612004)	None	Thrombocytopenia w/normal-sized platelets
FLI1	Bleeding disorder, platelet type 21 (OMIM 617443)	None	Thrombocytopenia w/large platelets

Table 2. continued from previous page.

Gene	Disorder [1]	Associated Malignancies	Hematologic Findings
RUNX1	Familial platelet disorder / acute myeloid leukemia	MDS/AML T-ALL Hairy cell leukemia	Thrombocytopenia (can have normal platelet counts)

AML = acute myeloid leukemia; AUL = acute undifferentiated leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; MDS = myelodysplastic syndrome; T-ALL = T-cell acute lymphoblastic leukemia
1. Disorders in this table are inherited in an autosomal dominant manner.

Management

Expert and consensus clinical guidelines for the management of inherited thrombocytopenia and leukemia predisposition syndromes, including those with germline *ETV6* pathogenic variants, have been proposed [Porter et al 2017, Dupuis & Gachet 2018].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ETV6* thrombocytopenia and predisposition to leukemia, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *ETV6* Thrombocytopenia and Predisposition to Leukemia

System/Concern	Evaluation	Comment
Hematologic/ Oncologic	CBC w/differential	Incl peripheral smear for detection of hematologic neoplasms
	Consider platelet aggregation studies.	If available & platelet count allows
	Consider bone marrow biopsy & aspirate.	Particularly if cytopenias are present on CBC
	Consider referral to hematologist/ oncologist.	Consider referral to a center w/expertise in predisposition to malignancy, as a multidisciplinary team may help refine optimal management.
Genetic counseling	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling, ideally in a center w/experience in predisposition to hematologic malignancy

CBC = complete blood count

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *ETV6* Thrombocytopenia and Predisposition to Leukemia

Manifestation/ Concern	Treatment	Considerations/Other
Clinical bleeding	Local measures	
	Antifibrinolytic agents; desmopressin	If bleeding is moderate or severe
	Platelet transfusion	For acute, moderate-to-severe bleeding [1]
Neoplasm	Standard neoplasm-specific therapy	Consider indications for stem cell transplantation, eligibility, & available donors. Confirm by targeted molecular genetic testing that potential related donors do not have *ETV6* thrombocytopenia w/predisposition to leukemia. [2]

1. Dupuis & Gachet [2018]
2. Godley [2014]

Prevention of Secondary Complications

For individuals with a history of moderate or severe bleeding, antifibrinolytic agents or desmopressin may be considered prior to surgical procedures to reduce bleeding complications. Platelet transfusions should be used judiciously – particularly in women of childbearing age – to reduce the risk of alloimmunization.

Surveillance

Individuals with *ETV6* thrombocytopenia and leukemia predisposition should adhere to published population-based cancer screening guidelines, including for breast and colon cancers. In addition to education regarding the signs and symptoms of hematologic malignancies, the following surveillance should be considered.

Table 5. Recommended Surveillance for Individuals with *ETV6* Thrombocytopenia and Predisposition to Leukemia

System/Concern	Evaluation	Frequency
Hematology/ Oncology	CBC w/differential	Every 6 to 12 mos [1, 2, 3]
	Bone marrow aspirate & biopsy [4]	Annually [1, 2]

CBC = complete blood count

1. The benefit of this screening regimen is currently unknown.

2. The frequency of such screening must be weighed against the burden of the screening protocol, particularly in young children. The frequency of CBC and bone marrow evaluations should be determined on a case-by-case basis by the physician and in consideration of patient/family preferences.

3. If changes in the CBC with differential are persistent for 2-4 weeks, particularly cytopenias, consider an additional bone marrow aspirate and biopsy.

4. To include morphology, cytogenetics, fluorescence in situ hybridization (FISH) (e.g., for chromosomes 5q, 7q, 8, and 20q) and molecular studies (depending on morphology, cytogenetics, and/or FISH) [Di Paola & Porter 2019].

Agents/Circumstances to Avoid

For individuals with *ETV6* thrombocytopenia and predisposition to leukemia and a history of bleeding, medications that decrease platelet function (e.g., aspirin, nonsteroidal anti-inflammatories) should be avoided. Similarly, participation in contact sports is not recommended.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of clinical surveillance for malignancy and management of potential significant thrombocytopenia.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Platelet counts should be monitored during pregnancy and prior to delivery, in collaboration with a hematologist. Platelet transfusions prior to invasive procedures (e.g., epidural analgesia or cæsarean section) or at the time of delivery may be considered in those with a history of bleeding or severe thrombocytopenia on a case-by-case basis.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

ETV6 thrombocytopenia and predisposition to leukemia is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- To date, all individuals diagnosed with *ETV6* thrombocytopenia and predisposition to leukemia have inherited an *ETV6* pathogenic variant from a heterozygous parent. In some families, the heterozygous parent did not have any known clinical findings associated with *ETV6* thrombocytopenia and predisposition to leukemia.
- *De novo ETV6* pathogenic variants have not been reported to date in *ETV6* thrombocytopenia and predisposition to leukemia.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.
- The family history of some individuals diagnosed with *ETV6* thrombocytopenia and predisposition to leukemia may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance of malignancies, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

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

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. A sib who inherits the *ETV6* pathogenic variant is expected to exhibit mild thrombocytopenia but may never develop leukemia due to the incomplete penetrance of the hematologic malignancies in this syndrome.
- If the *ETV6* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *ETV6* pathogenic variant but have no clinical findings of *ETV6* thrombocytopenia and predisposition to leukemia, the risk to the sibs of a proband appears to be low.

However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for the disorder because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *ETV6* thrombocytopenia and predisposition to leukemia has a 50% chance of inheriting the *ETV6* pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *ETV6* pathogenic variant, his or her family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the *ETV6* pathogenic variant in the family.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *ETV6* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Leukemia Research Foundation**
  191 Waukegan Road
  Suite 105
  Northfield IL 60093-2744
  Phone: 847-424-0600
  Email: info@lrfmail.org
  www.allbloodcancers.org
- **MedlinePlus**
  Thrombocytopenia

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. ETV6 Thrombocytopenia and Predisposition to Leukemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ETV6	12p13.2	Transcription factor ETV6	ETV6 database	ETV6	ETV6

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for ETV6 Thrombocytopenia and Predisposition to Leukemia (View All in OMIM)

600618	ETS VARIANT TRANSCRIPTION FACTOR 6; ETV6
601626	LEUKEMIA, ACUTE MYELOID; AML
616216	THROMBOCYTOPENIA 5; THC5

Molecular Pathogenesis

ETV6 has two start codons, one located at exon 1 and one located upstream of exon 3. Although two isoforms have been demonstrated to be expressed at the protein level, the function of the isoforms has not been evaluated. *ETV6* encodes transcription factor ETV6. There are three main domains:

- N-terminal pointed domain
- DNA binding domain located at the C terminus
- Linker region

ETV6 is a repressor of transcription, with critical roles in embryonic development and hematopoietic regulation [Hock et al 2004]. ETV6 is highly expressed in hematopoietic progenitor cells and is essential for hematopoiesis in the bone marrow [Di Paola & Porter 2019].

Mechanism of disease causation. Loss of function. The majority of pathogenic germline variants described to date have been located within the DNA binding domain at the C terminus. These are mostly loss-of-function missense variants, but nonsense and frameshift variants have also been identified. Single- and multiexon deletions have also been described and are thought to affect splice sites, resulting in truncation of the protein [Di Paola & Porter 2019].

Cancer predisposition. The molecular basis for predisposition to hematologic malignancy, specifically leukemias, in individuals with *ETV6* thrombocytopenia and predisposition to leukemia is not fully understood. Individuals with germline pathogenic *ETV6* variants and leukemias were not found to have a somatic hit on the second *ETV6* allele, though two cases have been reported with biallelic loss of *ETV6* [Topka et al 2015].

Table 6. Notable *ETV6* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_001987.4 NP_001978.1	c.641C>T	p.Pro214Leu	Recurrent pathogenic variant in 5 pedigrees [Di Paola & Porter 2019]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Cancer and Benign Tumors

Somatic variants involving *ETV6* are the most common type of cytogenetic finding in pediatric B-ALL. Specifically, the ETV6-RUNX1 fusion protein is identified in almost 25% of cases [Hunger & Mullighan 2015]. The other *ETV6* allele is often mutated suggesting a tumor-suppressive role for *ETV6* [Raynaud et al 1996]. In addition, *ETV6* is translocated, often with *NTRK3*, in several solid tumors including fibrosarcoma, secretory carcinoma of the salivary gland, and breast cancer [Biswas et al 2020].

Chapter Notes

Revision History

- 19 November 2020 (ma) Review posted live
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