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CEBPA-Associated Familial Acute Myeloid Leukemia (AML)

Synonym: *CEBPA*-Dependent Familial Acute Myeloid Leukemia

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Summary

Clinical characteristics

CEBPA-associated familial acute myeloid leukemia (AML) is defined as the presence of a heterozygous germline *CEBPA* pathogenic variant in an individual with AML and/or family in which more than one individual has AML. In contrast, sporadic *CEBPA*-associated AML is defined as AML in which a *CEBPA* pathogenic variant(s) is identified in leukemic cells but not in the non-leukemic cells. In the majority of individuals, the age of onset of familial AML appears to be earlier than sporadic AML; disease onset has been reported in persons as young as age 1.8 years and up to age 50 years. The prognosis of *CEBPA*-associated familial AML appears to be favorable compared with sporadic *CEBPA*-associated AML. Individuals with *CEBPA*-associated familial AML who have been cured of their initial disease may be at greater risk of developing additional independent leukemic episodes, in addition to the risk of relapse from preexisting clones.

Diagnosis/testing

The diagnosis of *CEBPA*-associated familial AML is established by identification of a heterozygous germline *CEBPA* pathogenic variant in a specimen that contains only non-leukemic cells from an individual and/or family with AML.

Management

Treatment of manifestations: Treatment usually includes cytarabine/anthracycline-based induction and cytarabine-based consolidation chemotherapy. Hematopoietic stem cell transplantation (HSCT) from a volunteer unrelated donor or appropriately screened family member should be reserved for individuals failing to achieve remission following standard induction therapy or for disease recurrence. Whenever possible, persons with AML should be treated as part of a clinical trial protocol.

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Surveillance: Similar to that for other forms of AML; because of the increased risk of late leukemia recurrence in persons with familial AML, lifelong surveillance is recommended. Asymptomatic individuals should have a CBC every six to 12 months and bone marrow examination for CBC abnormalities.

Agents/circumstances to avoid: Use of sib or related donors for HSCT without prior assessment of the germline *CEBPA* pathogenic variant in the donor.

Genetic counseling

Predisposition to *CEBPA*-associated familial AML is inherited in an autosomal dominant manner. Most individuals diagnosed with *CEBPA*-associated familial AML have had an affected parent who shares the germline pathogenic variant. Germline *CEBPA* pathogenic variants exhibit complete or near-complete penetrance for the development of AML in families reported to date. Each child of an affected individual has a 50% chance of inheriting the germline pathogenic variant. Prenatal testing for pregnancies at increased risk is possible if the germline *CEBPA* pathogenic variant in the family is known.

Diagnosis

Suggestive Findings

CEBPA-associated familial acute myeloid leukemia (AML) **should be suspected** in individuals with the following clinical and supportive laboratory findings.

Clinical findings

- Individuals with AML who also have a family history of AML
- Individuals who have developed AML at an early age (<50 years)

Supportive laboratory findings

- Typically, individuals with AML presenting before age 50 years with pathogenic variants in both copies of *CEBPA* (*CEBPA* double mutation [*CEBPA*dm]) in tumor DNA
- In the majority of individuals, a normal karyotype detected in leukemic cells
- A preponderance of French-American-British Cooperative Group AML Classification subtypes M1 or M2 as established by morphologic analysis of peripheral blood or bone marrow blasts
- Auer rods seen in blasts (i.e., abnormal, needle-shaped, or round, light blue- or pink-staining inclusions found in the cytoplasm of leukemic cells)
- Aberrant CD7 expression on blasts as demonstrated by flow cytometry

For this *GeneReview*, the following definitions apply:

- ***CEBPA*-associated familial AML** is defined by the presence of a heterozygous germline *CEBPA* pathogenic variant. A germline pathogenic variant may be inherited or *de novo*.
- **Sporadic *CEBPA*-associated AML** is defined as AML in which a somatic *CEBPA* pathogenic variant(s) is acquired in leukemic cells alone; these variants are absent in all of the individual's non-leukemic cells (see Molecular Genetics).

Establishing the Diagnosis

The diagnosis of *CEBPA*-associated familial AML **is established** in a proband with a heterozygous germline *CEBPA* pathogenic variant (see Table 1). Because *CEBPA*-associated familial AML develops from cells that have a pathogenic (cancer-predisposing) variant in both copies of *CEBPA*, leukemic cells frequently demonstrate both a germline and a somatic *CEBPA* variant. The germline pathogenic variant is typically a frameshift variant

located in the *CEBPA* region encoding the N-terminal C/EBPα protein, while the somatic pathogenic variant acquired in leukemic cells is typically in the region encoding the C terminal (see Molecular Genetics).

Note: In the literature, the terms *CEBPA*dm and *CEBPA*sm may be used. These terms refer to leukemic cells with biallelic *CEBPA* pathogenic variants ("*d*ouble *m*utation") or a heterozygous *CEBPA* pathogenic variant ("*s*ingle *m*utation"). These terms do not specify if the pathogenic variant is germline or somatic (see Molecular Pathogenesis).

Molecular testing approaches include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *CEBPA* is performed in a non-leukemic specimen.

  Note: (1) Testing for a germline pathogenic variant should not be performed on blood or bone marrow during active AML. Testing an uninvolved specimen, such as cells obtained by buccal swab/saliva, skin biopsy, or cultured dendritic cells, is imperative. (2) It should be noted that *CEBPA* pathogenic variants are found in the leukemic cells of approximately 9% of persons with AML (with heterozygous and biallelic pathogenic variants in similar proportions) [Green et al 2010, Dufour et al 2010, Fasan et al 2014]. However, few of these individuals have a germline *CEBPA* pathogenic variant. (3) Testing of blood or bone marrow during complete remission from AML may also be performed to detect a germline variant. The percentage of residual leukemic cells in remission samples is negligible, ensuring that somatic variants are not falsely classified as germline variants.

- **A multigene panel** that includes *CEBPA* and other genes of interest (see Differential Diagnosis) may also be considered, although care should be taken to ensure that coverage is adequate (due to the high GC content of the coding region: 75%) and that large insertions, such as those targeting the C terminal, are accurately detected with high-throughput methods. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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. (4) 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.

Table 1. Molecular Genetic Testing Used in *CEBPA*-Associated Familial Acute Myeloid Leukemia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
CEBPA	Sequence analysis [3]	100% (14/14 families) [4, 5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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. Sequencing of the coding region does not detect putative partial or complete gene deletions or variants in promoter regions. To date, however, no such germline *CEBPA* variants have been reported as causative of familial AML.
5. Smith et al [2004], Sellick et al [2005], Pabst et al [2008], Renneville et al [2009], Nanri et al [2010], Stelljes et al [2011], Taskesen et al [2011], Xiao et al [2011], Debeljak et al [2013], Tawana et al [2015], Pathak et al [2016], Yan et al [2016], Mendoza et al [2021]
6. 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.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

To date, fourteen families with *CEBPA*-associated familial acute myeloid leukemia (AML) have been reported [Smith et al 2004, Sellick et al 2005, Pabst et al 2008, Renneville et al 2009, Nanri et al 2010, Stelljes et al 2011, Taskesen et al 2011, Xiao et al 2011, Debeljak et al 2013, Tawana et al 2015, Pathak et al 2016, Yan et al 2016, Mendoza et al 2021], the majority of which manifest a highly penetrant (>80%) AML phenotype. More recently, germline *CEBPA* pathogenic variants located outside of the N terminal appear less penetrant, with approximately 50% of individuals with a heterozygous germline pathogenic variant developing AML. Given the limited number of family members tested in historical studies, it is possible that the true penetrance of AML may vary [Pabst & Mueller 2009].

The age of onset of *CEBPA*-associated familial AML is variable, but appears to be earlier than in sporadic AML. Disease onset has been reported in persons as young as 1.8 years [Debeljak et al 2013] and older than 45 years [Pabst et al 2008]. By contrast, the median age at diagnosis of persons with sporadic AML is 65 years.

Individuals commonly present with AML (of French-American-British subtypes M1, M2 or M4) following the acquisition of a somatic *CEBPA* pathogenic variant and additional somatic pathogenic variants, frequently involving *GATA2* (zinc finger 1), *WT1*, *TET2*, *EZH2*, and *NRAS* [Tawana et al 2015].

From an analysis of ten pedigrees with *CEBPA*-associated familial AML, the disease follows a course similar to sporadic AML with biallelic *CEBPA* pathogenic variants (*CEBPA*dm). The prognosis of individuals with familial AML appears to be favorable, with ten-year overall survival (OS) reaching 67%, compared to 54% OS in younger adults with sporadic AML associated with two *CEBPA* pathogenic variants and 29% OS with sporadic AML associated with a single *CEBPA* pathogenic variant [Tawana et al 2015].

Individuals with *CEBPA*-associated familial AML who have been cured of their initial disease may be at greater risk of developing recurrent, independent leukemic episodes that are characterized by a different somatic *CEBPA* pathogenic variant from that observed in the original tumor clone. This phenomenon contrasts with relapse in individuals with sporadic AML, where *CEBPA* pathogenic variants are stable throughout the disease course [Tiesmeier et al 2003, Shih et al 2006, Hollink et al 2011].

Genotype-Phenotype Correlations

To date, the majority of germline *CEBPA* pathogenic variants are frameshift variants located in the N terminal of the gene (preceding the internal start codon, located at codon 120).

Penetrance

Analysis of pedigrees reported to date suggests that germline *CEBPA* pathogenic variants exhibit high penetrance for the development of AML [Nickels et al 2013, Tawana et al 2015]. The penetrance of pathogenic variants may vary within and between families; data from ten families with germline *CEBPA* pathogenic variants affecting the N terminal (preceding the internal start codon, located at codon 120) revealed that more than 80% of confirmed or presumed obligate adult heterozygotes have developed disease to date [Tawana et al 2015]. Germline *CEBPA* pathogenic variants located outside of the N terminal (e.g., within the transactivation or leucine zipper domains) appear less penetrant, with approximately 50% of individuals with a heterozygous germline pathogenic variant developing AML [Pathak et al 2016, Mendoza et al 2021].

Nomenclature

International recognition of inherited hematologic malignancies has grown significantly following the WHO classification in 2016, which incorporated myeloid neoplasms associated with germline *ANKRD26*, *CEBPA*, *DDX41*, *GATA2*, and *RUNX1* pathogenic variants [Arber et al 2016]. The WHO classification also defined AML with biallelic *CEBPA* pathogenic variants (*CEBPA*dm [*CEBPA* double-mutated]) as a distinct prognostic entity. Of note, there was no distinction between sporadic and familial AML within this category.

Prevalence

CEBPA-associated familial AML is very rare, with only fourteen pedigrees reported [Smith et al 2004, Sellick et al 2005, Pabst et al 2008, Renneville et al 2009, Nanri et al 2010, Stelljes et al 2011, Taskesen et al 2011, Xiao et al 2011, Debeljak et al 2013, Tawana et al 2015, Pathak et al 2016, Mendoza et al 2021].

Taskesen et al [2011] identified a germline *CEBPA* pathogenic variant in five of 71 individuals (7%); two of the five had a family history of AML.

Genetically Related (Allelic) Disorders

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

Note: Sporadic *CEBPA*-associated acute myeloid leukemia (AML) is defined as AML in which a somatic *CEBPA* pathogenic variant(s) is acquired in leukemic cells alone and not in the germline (see Molecular Genetics).

Differential Diagnosis

The differential diagnosis for *CEBPA*-associated familial acute myeloid leukemia (AML) includes the following:

- Hereditary disorders associated with an increased risk of myeloid malignancy (e.g., *RUNX1* familial platelet disorder with associated myeloid malignancy, *DDX41*-associated familial myelodysplastic syndrome and acute myeloid leukemia)
- Sporadic AML with somatic *CEBPA* pathogenic variant(s)
- AML secondary to environmental exposures (e.g., benzene, radiation, chemotherapy)

Note: AML is a relatively rare disorder (~13,300 cases/year in the US); therefore, the more affected individuals in a family (and the closer the relationships), the greater the likelihood of a common cause (i.e., a heritable predisposition or a common exposure) [Owen et al 2008].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual newly diagnosed with *CEBPA*-associated familial acute myeloid leukemia (AML), the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with *CEBPA*-Associated Familial Acute Myeloid Leukemia

System/Concern	Evaluation	Comment
AYA/pediatric AML	Management of younger persons to be directed by relevant specialist teams (e.g., AYA or pediatric hematologists)	
AML / Assessment for suitable HSCT donor	HLA typing & virology tests (hepatitis A, B, C, & HIV)	
	CEBPA site-specific testing of family members at risk using either of the following: • Buccal, salivary, or skin DNA • Peripheral blood DNA in persons w/no history of preceding hematologic disease & normal CBC	Family members w/o an inherited *CEBPA* pathogenic variant may be offered HLA typing to assess their compatibility for stem cell donation to their affected relative.
Fertility	• Provide info re oocyte & sperm cryopreservation to persons of childbearing potential • Women: negative pregnancy test prior to commencing therapy	
CNS AML	LP if symptoms suggest CNS disease.	The timing of LP in AML is controversial.
Treatment-related heart disease	Cardiac scan in persons w/personal history of (or signs & symptoms suspicious for) heart disease & in those who have received previous anthracycline therapy	
Genetic counseling	• By genetics professionals [1] • Obtain a detailed family history & identify relatives who are obligate heterozygotes or potential heterozygotes for a *CEBPA* pathogenic variant & thus at risk for *CEBPA*-assoc familial AML.	To inform affected persons & their families re nature, MOI, & implications of *CEBPA*-assoc familial AML in facilitate medical & personal decision making
Family support/ resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.	

AYA = adolescent and young adult; AML = acute myeloid leukemia; CBC = complete blood count; CNS = central nervous system; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplantation; LP = lumbar puncture; MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Management of *CEBPA*-associated familial AML does not differ from that of sporadic *CEBPA*-associated AML [Döhner et al 2017] (see also NCCN Clinical Practice Guidelines in Oncology; no-fee registration and login required).

Treatment usually includes cytarabine/anthracycline-based induction and cytarabine-based consolidation chemotherapy with or without hematopoietic stem cell transplantation (HSCT) according to clinical, cytogenetic, and molecular risk. Specific treatment strategies are based on characteristics of the individual, response to chemotherapy, treatment setting, and protocol (if the individual is enrolled in a clinical trial). Note: Whenever possible, persons with AML should be treated as part of a clinical trial protocol.

Germline variants should be investigated and excluded in donors prior to consideration of HSCT using sib/related donors.

Supportive care includes blood products such as red blood cell and platelet transfusions as needed and treatment of infections with antibiotics.

Prophylactic antibiotics and antifungal agents are administered during periods of severe neutropenia including the consolidation and post-transplantation periods (NCCN Clinical Practice Guidelines in Oncology; no-fee registration and login required).

Relapses are treated with cytarabine-based salvage chemotherapy followed by allogeneic HSCT (if a suitable donor is available and if cure is the intent of treatment).

Surveillance

Affected individuals. Surveillance for *CEBPA*-associated familial AML is similar to that for other forms of AML. There are no generally accepted minimal residual disease (MRD) markers in *CEBPA*-associated AML.

Individuals are monitored and evaluated in accordance with administered treatment, clinical course, symptoms, and protocol, if enrolled in clinical trials. When complete remission is achieved and intensification therapy is complete, individuals are monitored with:

- CBC and platelet counts every one to three months for two years with the frequency decreasing to every three to six months for up to five years;
- Bone marrow aspiration when cytopenia and/or an abnormal peripheral blood smear are present.

Note: The use of flow cytometry for MRD monitoring is controversial.

Individuals with a germline *CEBPA* pathogenic variant who are cured of their initial disease episode may be at risk for new leukemic episodes, often occurring after a prolonged period of remission (>3 years post presentation) [Pabst et al 2009, Tawana et al 2015]. In light of these data, lifelong clinical surveillance is warranted to ensure prompt recognition and appropriate management of disease recurrence. Repeat testing of *CEBPA* in tumor DNA at AML recurrence is important to help distinguish conventional relapse from new, independent leukemic episodes.

Asymptomatic individuals with a germline *CEBPA* pathogenic variant:

- CBC every six to 12 months
- Bone marrow examination for those with CBC abnormalities

Agents/Circumstances to Avoid

Use of sib or related donors for HSCT without prior assessment of the germline *CEBPA* pathogenic variant in the donor should be avoided.

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 clinical monitoring.

Clinical monitoring may enable earlier diagnosis (and treatment) of AML, hence minimizing the risks associated with delayed presentation (e.g., severe anemia, neutropenic sepsis, and severe hemorrhage).

Note:

- There are currently no preemptive treatments available for asymptomatic individuals who have a germline *CEBPA* pathogenic variant.
- To date, all individuals with germline *CEBPA* pathogenic variants have presented with overt AML without any preceding blood count abnormalities or myelodysplasia; this is in contrast with other familial leukemia syndromes such as those associated with germline *RUNX1* or *GATA2* pathogenic variants [Tawana et al 2017].

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

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

Predisposition to *CEBPA*-associated familial acute myeloid leukemia (AML) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with *CEBPA*-associated familial AML inherited a *CEBPA* pathogenic variant from an affected parent.
- In rare cases, a proband may have a *de novo* germline *CEBPA* pathogenic variant.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- 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 *CEBPA*-associated familial AML may appear to be negative because of early death of a parent before the onset of AML or late onset of AML in a parent. Therefore, an apparently negative family history cannot be verified unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in 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 has the *CEBPA* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- The likelihood that a sib who inherits a familial *CEBPA* pathogenic variant will develop AML varies within and between families (ranging from ~50% to >80%) and appears to be significantly influenced by the site of the pathogenic variant (see Penetrance).
- If the germline *CEBPA* 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 *CEBPA* pathogenic variant but are clinically unaffected, sibs are still at increased risk for *CEBPA*-associated familial AML because (1) the germline pathogenic variant may demonstrate differences in disease manifestation and latency in a heterozygous parent, and (2) because of the theoretic possibility of parental somatic/germline mosaicism.

Offspring of a proband. Each child of an individual with *CEBPA*-associated familial AML has a 50% chance of inheriting the germline *CEBPA* pathogenic variant.

Other family members. The risk to other family members of inheriting the germline *CEBPA* pathogenic variant depends on the genetic status of the proband's parents: if a parent has the *CEBPA* pathogenic variant, his or her family members may be 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.

Testing of at-risk asymptomatic family members. If a germline *CEBPA* pathogenic variant has been identified in a family member with AML, molecular genetic testing may be offered to at-risk family members in order to determine the need for clinical surveillance (see Evaluation of Relatives at Risk).

Family planning

- The optimal time for determination of genetic risk in offspring of persons with known *CEBPA*-associated familial AML is before pregnancy. (Note: Molecular genetic *CEBPA* testing for the purpose of family planning is not recommended for individuals who develop AML in the absence of a molecular diagnosis of *CEBPA*-associated familial AML.)
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who have a molecular diagnosis of *CEBPA*-associated familial AML or who are at risk of having inherited a familial *CEBPA* pathogenic variant.

Prenatal Testing and Preimplantation Genetic Testing

Once a germline *CEBPA* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *CEBPA*-associated familial AML are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While use of prenatal testing is 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.

- **MedlinePlus**
  Familial acute myeloid leukemia with mutated CEBPA

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. CEBPA-Associated Familial Acute Myeloid Leukemia (AML): Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
CEBPA	19q13.11	CCAAT/enhancer-binding protein alpha	CEBPA	CEBPA

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 CEBPA-Associated Familial Acute Myeloid Leukemia (AML) (View All in OMIM)

116897	CCAAT/ENHANCER-BINDING PROTEIN, ALPHA; CEBPA
601626	LEUKEMIA, ACUTE MYELOID; AML

Molecular Pathogenesis

CEBPA encodes the CCAAT/enhancer-binding protein alpha (C/EBPα), a transcription factor that plays a key role in granulocyte development. A detailed review of the role of C/EBPα in human cancer has been published [Koschmieder et al 2009]. The role of mutation of *CEBPA* in the formation of acute myeloid leukemia (AML) is not well understood and is subject to ongoing research with several established mouse models simulating homozygous N-terminal frameshift pathogenic variants [Kirstetter et al 2008], combined N- and C-terminal pathogenic variants [Bereshchenko et al 2009], or conditional loss of C/EBPα [Ye et al 2013].

Initiation of translation at two in-frame AUG start codons (nucleotides 151-153 and 508-510) results in two C/EBPα protein isoforms with different lengths (see Table A, **Gene**). When translation initiates from the AUG at nucleotides 151-153, a 42-kd (also known as C/EBP-42) isoform a transcription factor is produced (NP_004355.2). The full-length 42-kd protein contains two distinct transactivation domains (that mediate contact with transcriptional apparatus), a C-terminal basic region (DNA-binding), and a leucine zipper for dimerization. Alternatively, when translation initiates from the alternative start site at AUG at nucleotides 508-510, a 30-kd (also known as C/EBP-30) isoform b is produced that lacks the first transactivation domain and impairs interaction with the transcriptional apparatus mediating cell-cycle progression (NP_001272758.1). While both isoforms are normally translated, the 42-kd isoform is more abundant.

All reported germline pathogenic variants are small deletions, duplications, or insertions before codon 120. These result in a frameshift causing premature truncation at the N-terminal region of the full-length C/EBPα protein, with preservation of the 30-kd isoform. The 30-kd isoform is believed to inhibit the action of the 42-kd isoform in a dominant-negative manner.

Mechanism of disease causation. Germline *CEBPA* pathogenic variants cause premature termination of the full-length C/EBPα protein, with preservation of the 30-kd isoform. The 30-kd isoform may inhibit the action of the normal 42-kd isoform (encoded by the remaining normal allele) in a dominant-negative manner. The acquisition of somatic in-frame insertions and deletions within the highly conserved C-terminal domains interferes with dimerization and DNA binding. The combination of N- and C-terminal pathogenic variants are thought to disrupt homo- and heterodimerization, cell cycle arrest, and differentiation [Pabst & Mueller 2009].

***CEBPA*-specific laboratory technical considerations.** *CEBPA* is a single-exon gene; the GC-rich coding region can interfere with PCR amplification and care should be taken to optimize diagnostic tests fully for sensitive and accurate detection of all variants.

Table 3. Notable Familial Acute Myeloid Leukemia-Associated *CEBPA* Germline Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Reference
NM_004364.5 NP_004355.2	c.68delC	p.Pro23ArgfsTer137	Smith et al [2004]
	c.68dupC	p.His24AlafsTer84	Sellick et al [2005], Renneville et al [2009], Tawana et al [2015]
	c.141delC	p.Ala48ProfsTer112	Pabst et al [2008]
	c.147_165del19	p.Glu50AlafsTer104	Debeljak et al [2013]
	c.158delG	p.Gly53AlafsTer107	Taskesen et al [2011]
	c.189delC	p.Asp63GlufsTer97	
	c.314_315insT	p.Phe106LeufsTer2	Pabst et al [2008]
	c.932A>C	p.Gln311Pro	Pathak et al [2016]
	c.442G>T	p.Glu148Ter	Mendoza et al [2021]

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 *CEBPA* pathogenic variants

- ***CEBPA*-associated familial AML.** The leukemic cells of most individuals with *CEBPA*-associated familial AML are compound heterozygous. In addition to the germline pathogenic variant in the N-terminal region, the leukemic cells commonly acquire somatic C-terminal in-frame pathogenic variant(s). Such variants disrupt the basic region and leucine zipper, impairing DNA binding as well as homo- and heterodimerization with other CEBP proteins and/or DNA binding [Pabst & Mueller 2007, Pabst & Mueller 2009].
- **Sporadic *CEBPA*-associated AML.** This is defined as AML in which a somatic *CEBPA* pathogenic variant(s) is acquired in leukemic cells alone and not in the germline. In 45%-55% of all persons with sporadic *CEBPA*-associated AML, two pathogenic *CEBPA* variants are detected (*CEBPA*dm); most frequently, a frameshift N-terminal variant is combined with a C-terminal in-frame insertion or deletion [Green et al 2010, Fasan et al 2014].
- *CEBPA* pathogenic variants have not been detected in solid tumors, although deregulation of *CEBPA* expression has been reported in liver, lung, and breast cancer, suggesting alternative mechanisms of abrogation [Lourenço & Coffer 2017].

Chapter Notes

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Revision History

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- 30 December 2009 (rdk) Original submission

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