|  |
| --- |
| Clinical Utility of MOLECULAR Testing in  AML with MUTATED *CEBPA*  Diagnostic Utility  Mutations in the transcription factor CCAATT-enhancer binding protein alpha (*CEBPA*) occur in approximately 5%-10% of *de novo* AML, with approximately half of these cases carrying biallelic mutations (*CEBPA*bi)1,2.  *CEBPA* mutation is a defining genetic abnormality in AML according to both the International Concensus Classification (ICC) (AML with in-frame bZIP *CEBPA* mutations when blasts ≥10%)3 and the 5th edition of WHO classification (AML with mutated *CEBPA* when blasts ≥20%)4.  Of note, AML with mutated *CEBPA* as defined by WHO 5th edition includes both biallelic (*CEBPA*bi) as well as single in-frame mutations located in the bZIP domain (*CEBPA*bZIP)4.  *CEBPA*bi is most commonly characterised by the combination of an N-terminal frameshift mutation and a C-terminal in-frame mutation usually affecting the basic leucine zipper (bZIP) domain.  AML with mutated *CEBPA* is frequently associated with a normal karyotype and aberrant CD7 expression on the myeloblasts2.  Genes commonly co-mutated in AML with mutated *CEBPA*include *TET2*, *GATA2*, *WT1*, *FLT3-*ITD, *CSF3R* and *NRAS*5.  AML with germline *CEBPA* mutation is typically characterised by an N-terminal germline *CEBPA* mutation and a C-terminal somatic *CEBPA* mutation, although rare germline C-terminal mutations have been described6,7.  Investigation for the possibility of a germline *CEBPA* mutation is warranted in cases where *CEBPA* mutations are biallelic and/or observed at a germline variant allele frequency.  Prognostic Utility  *CEBPA*bi mutation is associated with favourable outcomes in normal karyotype, *FLT3*-ITD-negative AML8-10.  Patients with *CEBPA*bZIP have recently been shown to have a favourable prognosis similar to those with *CEBPA*bi mutations1,11.  Co-mutations in *CEBPA*bi have been reported to impact outcome such as *TET2* (inferior) and *GATA2* (favourable) however this is not consistent across all studies1,5,11,12.  References  **1.** Taube F, et al. CEBPA Mutations in 4708 Patients with Acute Myeloid Leukemia - Differential Impact of bZIP and TAD Mutations on Outcome. *Blood* 2021. **2.** Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition). Lyon: IARC; 2017. **3.** Arber DA, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemia: Integrating Morphological, Clinical, and Genomic Data. *Blood* 2022. **4.** Khoury JD, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia* 2022. **5.** Wilhelmson AS, Porse BT. CCAAT enhancer binding protein alpha (CEBPA) biallelic acute myeloid leukaemia: cooperating lesions, molecular mechanisms and clinical relevance. *Br J Haematol* 2020; **190**(4): 495-507. **6.** Pabst T, et al. Somatic CEBPA mutations are a frequent second event in families with germline CEBPA mutations and familial acute myeloid leukemia. *J Clin Oncol* 2008; **26**(31): 5088-93. **7.** Pathak A, et al. Whole exome sequencing reveals a C-terminal germline variant in CEBPA-associated acute myeloid leukemia: 45-year follow up of a large family. *Haematologica* 2016; **101**(7): 846-52. **8.** Green CL, et al. Prognostic significance of CEBPA mutations in a large cohort of younger adult patients with acute myeloid leukemia: impact of double CEBPA mutations and the interaction with FLT3 and NPM1 mutations. *J Clin Oncol* 2010; **28**(16): 2739-47. **9.** Wouters BJ, et al. Double CEBPA mutations, but not single CEBPA mutations, define a subgroup of acute myeloid leukemia with a distinctive gene expression profile that is uniquely associated with a favorable outcome. *Blood* 2009; **113**(13): 3088-91. **10.** Fasan A, et al. The role of different genetic subtypes of CEBPA mutated AML. *Leukemia* 2014; **28**(4): 794-803. **11.** Tarlock K, et al. CEBPA-bZip mutations are associated with favorable prognosis in de novo AML: a report from the Children’s Oncology Group. *Blood* 2021; **138**(13): 1137-47. **12.** Grossmann V, et al. CEBPA double-mutated acute myeloid leukaemia harbours concomitant molecular mutations in 76·8% of cases with TET2 and GATA2 alterations impacting prognosis. *British Journal of Haematology* 2013; **161**(5): 649-58. |