SJIF Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 8.
Issue: 11
Page N. 4-9
Year: 2024

Review Article www.wjahr.com

GENETIC MARKERS: ADVANCEMENT TOWARDS COMPREHENDING ACUTE MYELOID LEUKEMIA

Ekta A. Andriyas[1], Neha Pant[1], Neetu Kushwaha[1], Deepak Sharma[2], Arun Kumar Saxena[2], Munzali Hamisu Umar[2] and Imran Hussain[3]*

[1]Department of Medical Laboratory Technology, Faculty of Allied Health Sciences, Era University, Lucknow, U.P, India – 226003.
[2]Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, Integral University, Lucknow, U.P, India – 226026.
[3]Assistant Professor & Head, Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, Integral University, Lucknow, U.P, India – 226026.

Article Received date: 04 September 2024 **Article Revised date:** 24 September 2024 **Article Accepted date:** 14 October 2024

***Corresponding Author: Imran Hussain**
Assistant Professor & Head, Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, Integral University, Lucknow, U.P, India – 226026.

1. INTRODUCTION

The malignant tumor known as acute myeloid leukemia (AML) affects hemopoietic stem cells and progenitor cells. It is typified by an irregular proliferation of primitive cells in the bone marrow and peripheral circulation. Anaemia, bleeding, infection, and organ infiltration are among the clinical signs and symptoms of acute myeloid leukemia. An increased frequency of AML has been seen over time, men have been more likely than women to have AML, and the disease's incidence has been rising. Currently, the most significant predictors of AML outcomes are still cytogenetic and molecular abnormalities. These parameters are tightly linked to clinical characteristics such as age, white blood cell count and morphology, treatment response, recurrence rate, and overall survival (OS). The World Health Organisation (WHO) and European Leukaemia Net (ELN) have developed illness prognostic classification on the strong basis of this. Currently, less than 50% of adult AML patients will survive for five years; this percentage is much lower for older patients. According to statistics, patients over 65 have a median overall survival of less than a year. This article outlines the molecular indicators associated with AML and their clinical significance for early diagnosis and prognosis. Prognostic indicators can gauge the severity of a patient's condition and forecast their long-term results, while predictive markers facilitate the tracking of therapy response and recurrence.

1. Specific Molecules Associated with Gene Mutations

1.1 Nucleophosmin 1

The most prevalent gene mutation associated with AML is NPM1 mutation. NPM1, found on chromosome on the long arm of chromosome 5, encodes a multipurpose chaperone protein that travels back and forth between the cytoplasm and nucleus. NPM1 primarily controls the assembly and trafficking of ribosomal proteins, the stabilization of the p53 and p19ARF tumor suppressor pathways, the DNA repair process, the integrity of the genome, and, in the end, DNA transcription regulation through chromatin structural modifications. Any mutation that impairs its normal function as a tumor suppressor will cause normal cells to become malignant. Furthermore, in healthy cells, the wild-type NPM1 protein localizes to the nucleolus. Though its precise mechanism is yet unknown, the mutant protein typically mislocalizes to the cytoplasm, which is directly linked to the pathophysiology of leukemia.[6] According to ELN guidelines, patients with NPM1 mutations and an allelic ratio (AR) < 0.5 for FMS, such as those with tyrosine kinase 3-internal tandem replication (FLT3-ITD), have a favorable prognosis. Following the initial complete remission, allogeneic hematopoietic stem cell transplantation, or allo-HSCT, is not advised. NPM1-mutant patients without FLT3-ITD or with FLT3-ITDlow are placed in the good prognosis group, while patients with NPM1-mutation and FLT3-ITDhigh are placed in the intermediate prognosis group, per the 2021 National Comprehensive Cancer Network (NCCN) criteria. Consequently, it is believed that leukemogenesis is associated with other cellular and molecular genetic alterations, such as FLT3-ITD, and is not only caused by NPM1 mutation. It has been seen that isocitrate dehydrogenase 1/2 (IDH1/2) and DNA methyltransferase

3 alpha (DNMT3A) mutations, when combined with the NPM1 mutation, resulted in a poor prognosis. It is generally accepted that these mutations are secondary to the NPM1 mutation. As with promyelocytic leukemia-retinoic acid receptor a (PML-RARA) rearrangement, NPM1 can be used as a marker for monitoring minimal residual disease (MRD) in patients with acute myeloid leukaemia (AML). In other words, in patients exhibiting morphological full remission, an increase in mutant NPM1 in peripheral blood is indicative of an impending AML relapse. Therefore, in accordance with the NPM1 level in MRD, prompt and appropriate intervention can be implemented. It is currently understood that the combined administration of arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) can further trigger the death of AML cells by degrading the mutant NPM1 protein in patients with NPM1 mutation.[7] Large-scale basic studies are still required to investigate the role and mechanism of NPM1 in order to establish a new theoretical foundation for the treatment of AML, as our understanding of the mechanism of targeted therapies based on NPM1 is still lacking.

1.2 FLT 3

FLT3 belongs to the type III receptor tyrosine kinase (RTK) family and is situated on the long arm of chromosome 13. It contributes to hematopoietic cell division, proliferation, and death via the extracellular domain that has ligand binding sites. Tyrosine kinase domain (TKD) point mutations account for just 7% of AML cases, while FLT3 mutations account for roughly 30% of cases. ITD accounts for approximately 25% of AML cases. The prognosis is poor because FLT3-ITD is typically frequent in AML with a normal karyotype. Mutant FLT3 molecularly stimulates downstream components of the RAS/MAPK, PI3K, and STAT5 signaling pathways. Relevant statistical data indicated that the expression level of FLT3 was connected with various National Comprehensive Cancer Network (NCCN) stratifications of AML in terms of clinical characteristics, with the M3 subtype having the lowest level and the M5 subtype having the greatest level. Numerous investigations have demonstrated that individuals with FLT3 mutations primarily exhibit high peripheral blood white blood cell counts, high myeloid progenitor cell counts, and a poor prognosis.[8,10] Of these, patients with FLT3-ITD are more likely to experience coupled PML RARA rearrangement, a condition that is uncommon in patients with complex karyotypes or core binding factor (CBF)-AML. FLT-ITD patients have a significantly worse prognosis and worse OS and event-free survival (EFS) as compared to FLT-TKD patients. A study revealed a strong correlation between the expression ratio of the mutant FLT3 allele relative to the wild-type FLT3 allele and the prognosis of FLT3-mutant patients. The duration of remission (DOR), OS, and EFS decrease with increasing ratio. Thus, the relative amount of mutant alleles was measured using DNA fragment analysis techniques, and a cutoff value was established to differentiate between various prognostic categories.[11] Small molecule tyrosine kinase inhibitors, such as sorafenib, sunitinib, and midostaurin, have been used to treat AML with FLT3 mutations by blocking the FLT3 signaling pathway and specifically destroying leukemia cells. When compared to conventional chemotherapy, a multitude of clinical trials conducted in recent years have demonstrated significant improvements in the therapeutic benefit of multitarget small molecule tyrosine kinase inhibitors on patients with AML. Drug resistance, however, means that the DORs of these medications alone are still insufficient, and the combination of these medications with other chemotherapeutic treatments is now the recommended course of action for treating this kind of AML.

1.3 CCAAT Enhancer Binding Protein Alpha

On chromosome 19, the long arm contains the CEBPA gene. The leucine zipper-containing transcription factor CEBPA protein has three structural regions: the DNA-binding region, the transcriptionally active area at the N terminus, and the leucine-rich dimerization functional region at the C terminus. Out-of-frame insertions or deletions at the N-terminus and in-frame insertions or deletions at the C-terminus are the two different forms of CEBPA mutations. The CEPBP mutation on both alleles of chromosome 19 is referred to as the CEBPA double mutation (biCEBPA). Hematopoietic myeloid cell differentiation is significantly influenced by CEBPA. CEBPA mutations are present in about 10% of AML patients and 7–15% of AML patients with normal karyotypes. The majority of them are M2 types, and they have a typically good prognosis. In the 2016 WHO classification of hematopoietic and lymphoid neoplasms, a novel molecular biological feature known as "AML with biCEBPA" was identified as a clinical subtype of AML. The early screening of CEBPA mutations is also advised by the ELN guidelines. BiCEBPA was positively correlated with improved prognosis, as demonstrated by multicenter clinical data that compared with all AML patients, it was significantly correlated with improved EFS and OS when receiving cytarabine-based chemotherapy, with hazard ratios (HR) of 0.41 and 0.37, respectively. However, biCEBPA was not correlated with consolidation strategies like HSCT. The prognosis is relatively poor when combined with TET2 mutations.[12,13] It's interesting to note that sequencing analysis of normal karyotype AML patients with CEBPA mutations in recent years has revealed that Tet methylcytosine dioxygenase 2 (TET2) and GATA2 mutations are more likely to occur in biCEBPA patients (approximately 30%). On the other hand, CEBPA single mutation (moCEBPA) patients are more likely to have combined NPM1, FLT-ITD/TKD, and IDH2 mutations. While CEBPA has not yet been found to be a sign of MRD, the particular immunophenotype linked to biCEBPA may prove to be a useful tool for monitoring treatment outcomes and diagnosing diseases. In this case, the GATA2 mutation deserves special attention. GATA2 might be a new gene that predisposes people to familial AML (14). Known to be a haematopoietic "stem" gene,

GATA2 is highly expressed in haematopoietic stem cells and necessary for the production of mast cells and megakaryocytes. During myeloid development, GATA2 is down-regulated, necessitating overexpression to prevent this differentiation. The identification of a GATA2 mutation in the AML susceptibility family offers a fresh approach to investigating the mechanism by which GATA2 induces leukaemia and could elucidate its function in preserving "stem." In cases of AML, patients with GATA2 mutations had a dismal outcome. Bravely, it might be appropriate to employ proactive treatment plans for family members who have GATA2 mutations before symptoms appear.

2. The Molecules Associated with Abnormalities in Chromosomal Position

2.1 PML RARA

A fusion gene produced by the t (14; 16) (q24; q21) translocation codes for PML-RARA. It is a significant molecular characteristic of APL that is seen in about 98% of individuals.[15] One of PML-RARA's two main mechanisms of action in APL is the deregulatory regulation of transcription.[16] PML is primarily engaged in the control of signaling pathways, as well as the stimulation of the transcription of the proapoptotic protein Bim and the cell cycle inhibitor p27Kip. The RARA gene, which is found on 17q21, codes for a nuclear receptor that, when its ligand, retinoic acid, is present, stimulates transcription and causes the induction of numerous target genes that are important in differentiation. The heterodimer RAR-RXR, which is made up of RARA and retinoic acid X receptor a (RXRA), is a transcriptional activator complex that is necessary for promyelocyte differentiation.[17] RAR-RXR functions as a transcriptional repressor in the absence of retinoic acid by enlisting the help of the accessory repressors DNMT1, DNMT3A, histone deacetylase, and histone methyltransferase as well as taking part in chromatin remodeling. RAR-RXR experiences a conformational shift in the presence of retinoic acid, which causes RAR-RXR to dissociate and activates genes necessary for primitive cell differentiation. The PML and RARA proteins can fuse together to obstruct the recruitment of coactivators and stop the transcription of retinoic acid response elements.[18] Therefore, etiological research and patient management optimisation both greatly benefit from PML-RARA screening for patients with probable APL. PML-RARA mutations can be identified through fluorescence in situ hybridisation (FISH) or real-time quantitative polymerase chain reaction (RT−qPCR). These methods not only aid in diagnosis and treatment, but also measure changes in MRD, which is crucial for prognostic assessment, monitoring recurrence, and figuring out when to stop taking medication. But as of right now, over ten fusion genes containing distinct RARA counterparts have been discovered in between 1% and 2% of APL patients. Among these is ZBTB16-RARA (PLZF-RARA), the most common molecular variant associated with APL[19], the RARA gene was rearranged with NPM1, NUMA1, STAT5B, PRKAR1A, FIP1L1, BCOR, NABP1, TBL1XR1, GTF2I, IRF2BP2, and FNDC3B, among others; the majority of these were not affected by ATRA or ATO.[20] Therefore, if APL patients have these types of fusion genes found in them, it would seem that their chances of receiving an effective ATRA and ATO treatment are slim.

2.2 CBF

The cytogenetically defined CBF mutations in AML are represented by t (8; 21) or inv (16)/t (16; 16), resulting in the production of the fusion proteins CFB b subunit-myosin heavy chain 11 (CBFb-MYH11) or RUNX1-RUNX1T1 (AML1 ETO), respectively.[21] About 15% of adult AML cases and 30% of paediatric AML cases are thought to be caused by CBF mutations, making them one of the most prevalent cytogenetic alterations in AML patients. Relevant research has demonstrated that leukaemia cannot be induced just by CBFb-Myh11 and AML1-ETO mutations. The "double hit" paradigm, which posits that AML1-ETO, CBFb-MYH11, CCND1, and CCND2 molecular genetic changes play significant roles in the aetiology of CBF-AML, is already entirely accepted.[22,23]

Leukaemia frequently results in the t (8; 21) (q22; q22) translocation, which produces an AML1-ETO fusion protein. Another name for the AML1 (RUNX1) protein family is CBFa. It is made up of a collection of heterodimeric transcription factors, with the b subunit (CBFb) encoded by CBFb and the a subunit (CBFa) encoded by three distinct genes, RUNX1/RUNX2/RUNX3. RUNX1 plays a crucial role in the differentiation of haematopoietic cells and the formation of myeloid cells at the molecular level, while ETO (RUNX1T1) mostly helps with transcriptional repression by enlisting corepressors. As a transcriptional repressor, AML1-ETO impedes normal haematopoietic cell differentiation, increases leukaemia progression, and directly prevents the transcription of AML1-dependent tumour suppressors. Furthermore, it interferes with the regular haematopoietic process by suppressing the function of haematopoietic transcription factors as PU1, GATA1, and CEBPA. Five to ten percent of all AML cases, including seven to twelve percent of adult AML cases, are T (8; 21)-positive. It is uncommon in the M1 and M4 subtypes but prevalent in the AML-M2 subtype. Longer median OS, a higher remission rate, and a generally better prognosis are the clinical characteristics. One of the key synergistic variables in the pathophysiology of t (8;21)-positive AML is the most prevalent mutation in the disease, c-Kit, which accounts for 20–25% of newly diagnosed cases. The NCCN guidelines place CBF-AML with a c-Kit mutation in the intermediate prognosis category. Encoding the CBFb-MYH11 fusion protein is the fusion gene CBFb-MYH11, which is produced by chromosome 16 inversion inv (16) (p13; q22). CBFb-MYH11 functions as a transcriptional repressor and collaborates with AML1 to limit the transcription of PTEN, Bcl-2, CEBPA, ARF, and PSGL-

1. At the RUNX binding site on DNA, CBFa and CBFb normally form a CBFa/CBFb complex that controls gene expression. The C-terminus of MYH11 connects with the CBFb residue during gene rearrangement. Due to its isomeric nature to RUNX1 (CBFa), the CBFb-MYH11 fusion protein disrupts the regular operation of the CBFa/CBFb complex via competitive inhibition. One important regulator of hematopoiesis is CBFa. Its normal function will be harmed and abnormal fusion products will inhibit hematopoietic cell differentiation. FISH and RT-qPCR are currently sensitive and useful methods for finding these rearrangement mutations.[24,25]

2.3 Histone lysine Methyltransferase 2A (KMT2A)

KMT2A is found on human chromosome 11's long arm, in region 2 band 3 (11q23). It belongs to the family known as the trithorax group (TrxG). KMT2A can be rearranged via translocation, deletion, insertion, inversion, and partial tandem duplication; translocation is the most frequent rearrangement and was initially described by Ziemin-van der Poel et al. in 1991.[26] Armstrong et al.[27] discovered in 2002 that KMT2A encodes a transcription factor that controls gene expression in the early stages of embryonic development and the differentiation of hematopoietic cells. The transcription of homeotic genes (HOX) is activated by methylating the lysine residue at histone H3's fourth position, which is accomplished by the SET region's methyltransferase activity. Hematopoietic cells, such as stem cells and progenitor cells, have widespread expression of KMT2A. It requires the fusion of several partner genes, including AF4, AF9, ENL, AF10, and ELL, before it exhibits leukemogenic effects.[28] MEN1 and LEDGF bind to the N-terminus of KMT2A, activating HOXA9 and HOXA10 in the process. These genes are typically increased in leukemias when KMT2A mutations occur. 43-58% of instances of newborn AML, 39% of cases in children under the age of two, 8-9% of cases in children over two, and roughly 5% of cases in adult AML are explained by KMT2A rearrangement.[29] KMT2A rearrangement is often less common as people age and is roughly four times more common in children than in adults. In 5–10% of AML cases connected to topoisomerase II inhibitor therapy, KMT2A rearrangements are seen. Due to their high risk of recurrence and low rate of remission, these patients typically have a poor prognosis.[30] Research indicates that following remission, allo-HSCT may lower the mortality risk and relapse rate in AML patients with KMT2A rearrangement.[31] Nevertheless, there are drawbacks to allo-HSCT, including a shortage of donors and difficult transplanting circumstances. Scientists have recently concentrated on investigating medications that target fusion protein-mediated transcription. Using high-throughput sequencing, Grembecka et al. screened two small molecule inhibitors, MI-2 and MI-3, and discovered that they interfered with MEN1's binding to KMT2A, preventing the KMT2A-AF9 fusion protein from binding to the target gene promoter.[32] It is anticipated that the development of further medications that target the fusion protein will offer a novel approach to treating AML with a KMT2A mutation.

3. Non-coding RNAs represented by miRNAs

Small RNA molecules called microRNAs (miRNAs) are made up of 17–25 nucleotides. They are primarily engaged in the post-transcriptional regulation of mRNA and have a significant impact on apoptosis, differentiation, and cell proliferation. A range of malignant tumors exhibit aberrant expression of distinct subtypes of miRNAs, which exhibit tissue selectivity. miRNAs are highly stable and resistant to RNase destruction in blood. Their expression level in blood is connected to the type, stage, grade, and prognosis of cancers. Ma et al.[33] demonstrated that cytogenetically normal AML (CN-AML) patients with high expression of miR-362-5p had shorter overall survival (OS) compared to the control group, suggesting that miR-362-5p has an oncogenic role in AML. Additionally, this study raised the possibility that miR-362-5p functions as a stand-alone poor prognostic factor for CN-AML. According to Zhang et al.[34], the expression of mir-216b dramatically decreased following chemotherapy to achieve complete remission and significantly increased following recurrence. It was also shown that mir 216b overexpression was linked to poor prognosis and chemotherapy efficacy in AML patients. Mir-3151 is situated inside the BAALC gene's first intron.[35] Only CN-AML patients older than 60 were enrolled in the trial, and mir-3151 had been discovered to be a separate predictive factor.[36] Dıaz-Beyaet et al. study from 1956 revealed that AML patients with increased mir-3151 expression showed a greater cumulative recurrence rate and a shorter OS. Regardless of a patient's gender, Aleksandra et al.[37] found that miR-204 expression was dramatically downregulated in AML patients and significantly elevated after effective treatment (daunorubicin + cytarabine). Following induction chemotherapy, the CRR was greater in AML patients with elevated miR-204. As a result, miR-204 is anticipated to be used as a biomarker for AML prognostic assessment.[38] Hu et al.[39] proposed that a positive outcome was associated with high expression of miR-98 in individuals with AML who had only received chemotherapy. In summary, the aforementioned findings indicated that miRNAs are anticipated to develop into biomarkers for the initial diagnosis, prognostic assessment, and screening of AML; nevertheless, numerous clinical difficulties still need to be investigated further.

REFERENCES

1. Yi M, Li A, Zhou L, Chu Q, Song Y, Wu K. The global burden and attributable risk factor analysis of acute myeloid leukemia in 195 countries and territories from 1990 to 2017: Estimates based on the global burden of disease study 2017. J Hematol Oncol, 2020; 13(1): 72. doi: 10.1186/s13045-020-00908-z

2. Wiatrowski K, Kim TH, Przespolewski A. Cellular and molecular biomarkers predictive of response to immunotherapy in acute myeloid leukemia. Front Oncol., 2022; 12: 826768. doi: 10.3389/fonc.2022.826768
3. Kayser S, Levis MJ. Clinical implications of molecular markers in acute myeloid leukemia. Eur J Haematol., 2019; 102(1): 20–35. doi: 10.1111/ejh.13172
4. Prada-Arismendy J, Arroyave JC, Röthlisberger S. Molecular biomarkers in acute myeloid leukemia. Blood Rev., 2017; 31(1): 63–76. doi: 10.1016/j.blre.2016.08.005
5. Riva L, Luzi L, Pelicci PG. Genomics of acute myeloid leukemia: The next generation. Front Oncol., 2012; 2: 40. doi: 10.3389/fonc.2012.00040
6. Dawson MA, Gudgin EJ, Horton SJ, Giotopoulos G, Meduri E, Robson S, et al. Recurrent mutations, including NPM1c, activate a BRD4-dependent core transcriptional program in acute myeloid leukemia. Leukemia., 2014; 28(2): 311–20. doi: 10.1038/ leu.2013.338
7. El Hajj H, Dassouki Z, Berthier C, Raffoux E, Ades L, Legrand O, et al. Retinoic acid and arsenic trioxide trigger degradation of mutated NPM1, resulting in apoptosis of AML cells. Blood., 2015; 125(22): 3447–54. doi: 10.1182/blood-2014-11-612416
8. Bienz M, LudwigM, Leibundgut EO, Mueller BU, Ratschiller D, Solenthaler M, et al. Risk assessment in patients with acute myeloid leukemia and a normal karyotype. Clin Cancer Res., 2005; 11(4): 1416–24. doi: 10.1158/1078-0432.CCR-04-1552
9. Nitika WJ, Hui AM. Role of biomarkers in FLT3 AML. Cancers (Basel)., 2022; 14(5): 1164. doi: 10.3390/cancers14051164
10. Santos FP, Jones D, Qiao W, Cortes JE, Ravandi F, Estey EE, et al. Prognostic value of FLT3 mutations among different cytogenetic subgroups in acute myeloid leukemia. Cancer, 2011; 117(10): 2145–55. doi: 10.1002/cncr.25670
11. Zaidi SZ, Owaidah T, Al Sharif F, Ahmed SY, Chaudhri N, Aljurf M. The challenge of risk stratification in acute myeloid leukemia with normal karyotype. Hematol Oncol Stem Cell Ther., 2008; 1(3): 141–58. doi: 10.1016/s1658-3876(08)50023-9
12. Li HY, DengDH, HuangY, YeFH, HuangLL, XiaoQ, etal. Favorable prognosis of biallelic CEBPA gene mutations in acute myeloid leukemia patients: a meta-analysis. Eur J Haematol., 2015; 94(5): 439–48. doi: 10.1111/ejh.12450
13. Greif PA, Dufour A, Konstandin NP, Ksienzyk B, Zellmeier E, Tizazu B, et al. GATA2 zinc finger 1 mutations associated with biallelic CEBPA mutations define a unique genetic entity of acute myeloid leukemia. Blood., 2012; 120(2): 395–403. doi: 10.1182/blood-2012-01-403220
14. Hahn CN, Chong CE, Carmichael CL, Wilkins EJ, Brautigan PJ, Li XC, et al. Heritable GATA2mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia. Nat Genet., 2011; 43(10): 1012–7. doi: 10.1038/ng.913
15. De Braekeleer E, Douet-Guilbert N, De Braekeleer M. RARA fusion genes in acute promyelocytic leukemia: A review. Expert Rev Hematol., 2014; 7(3): 347–57. doi: 10.1586/ 17474086.2014.903794
16. Noguera NI, Catalano G, Banella C, Divona M, Faraoni I, Ottone T, et al. Acute promyelocytic leukemia: Update on the mechanisms of leukemogenesis, resistance and on innovative treatment strategies. Cancers (Basel)., 2019; 11(10): 1591. doi: 10.3390/ cancers11101591
17. Nagpal S, Friant S, Nakshatri H, Chambon P. RARs and RXRs: evidence for two autonomous transactivation functions (AF-1 and AF-2) and heterodimerization in vivo. EMBO J., 1993; 12(6): 2349–60. doi: 10.1002/j.1460-2075.1993.tb05889.x
18. Jimenez JJ, Chale RS, Abad AC, Schally AV. Acute promyelocytic leukemia (APL): a reviewof the literature. Oncotarget, 2020; 11(11): 992–1003. doi: 10.18632/ oncotarget.27513
19. Baba SM, Pandith AA, Shah ZA, Baba RA. Pathogenetic implication of fusion genes in acute promyelocytic leukemia and their diagnostic utility. Clin Genet., 2019; 95: 41–52. doi: 10.1111/cge.13372
20. Liquori A, Ibañez M, Sargas C, Sanz MA, BarraganE, Cervera J. Acute promyelocytic leukemia: A constellation of molecular events around a single PML RARA fusion gene. Cancers (Basel)., 2020; 12(3): 624. doi: 10.3390/cancers12030624
21. Mosna F, Gottardi M. Stem cell modeling of core binding factor acute myeloid leukemia. Stem Cells Int., 2016; 2016: 7625827. doi: 10.1155/2016/7625827
22. Gilliland DG. Molecular genetics of human leukemias: new insights into therapy. Semin Hematol., 2002; 39(4 Suppl 3): 6–11. doi: 10.1053/shem.2002.36921
23. Rau RE. Beyond KIT in CBF-AML: chromatin and cohesin. Blood., 2016; 127(20): 2370–1. doi: 10.1182/blood-2016-03-707083
24. Gulley ML, Shea TC, Fedoriw Y. Genetic tests to evaluate prognosis and predict therapeutic response in acute myeloid leukemia. JMol Diagn, 2010; 12(1): 3–16. doi: 10.2353/jmoldx.2010.090054
25. Lagunas-Rangel FA, Chavez-Valencia V, Gomez-Guijosa MA, Cortes-Penagos C. Acute myeloid leukemia-genetic alterations and their clinical prognosis. Int J Hematol Oncol Stem Cell Res., 2017; 11(4): 328–39.
26. Ziemin-van der Poel S, McCabe NR, Gill HJ, Espinosa R3rd, Patel Y, Harden A, et al. Identification of a gene, MLL, that spans the breakpoint in 11q23 translocations associated with human leukemias. Proc Natl Acad Sci USA, 1991; 88(23): 10735–9. doi: 10.1073/pnas.88.23.10735

27. Armstrong SA, Staunton JE, Silverman LB, Pieters R, den Boer ML, Minden MD, et al. MLL translocations specify a distinct gene expression profile that distinguishes a unique leukemia. Nat Genet., 2002; 30(1): 41–7. doi: 10.1038/ng765
28. Menghrajani K, Gomez-Arteaga A, Madero-Marroquin R, Zhang MJ, Bo-Subait K, Sanchez J, et al. Risk classification at diagnosis predicts post-HCT outcomes in intermediate-, adverse-risk, and KMT2A-rearranged AML. Blood Adv., 2022; 6(3): 828. doi: 10.1182/bloodadvances.2021004881
29. Mann G, Attarbaschi A, Schrappe M, De Lorenzo P, Peters C, Hann I, et al. Interfant-99 study group. improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage-leukemia (MLL)-rearranged acute lymphoblastic leukemia: Results from the interfant-99 study. Blood., 2010; 116(15): 2644–50. doi: 10.1182/blood-2010-03-273532
30. Schoch C, Schnittger S, Klaus M, Kern W, Hiddemann W, Haferlach T. AML with 11q23/MLL abnormalities as defined by the WHO classification: incidence, partner chromosomes, FAB subtype, age distribution, and prognostic impact in an unselected series of 1897 cytogenetically analyzed AML cases. Blood., 2003; 102(7): 2395–402. doi: 10.1182/blood-2003-02-0434
31. Pigneux A, Labopin M, Maertens J, Cordonnier C, Volin L, SocieG, et al. Acute leukemia working party EBMT. outcome of allogeneic hematopoietic stem-cell transplantation for adult patients with AML and 11q23/MLL rearrangement (MLL-r AML). Leukemia, 2015; 29(12): 2375–81. doi: 10.1038/leu.2015.143
32. Shi A, Murai MJ, He S, Lund G, Hartley T, Purohit T, et al. Structural insights into inhibition of the bivalent menin-MLL interaction by small molecules in leukemia. Blood., 2012; 120(23): 4461–9. doi: 10.1182/blood-2012-05-429274
33. Zhang TJ, Wu DH, Zhou JD, Li XX, Zhang W, Guo H, et al. Overexpression of miR-216b: Prognostic and predictive value in acute myeloid leukemia. J Cell Physiol., 2018; 233(4): 3274–81. doi: 10.1002/jcp.26171
34. Stark MS, Tyagi S, Nancarrow DJ, Boyle GM, Cook AL, Whiteman DC, et al. Characterization of the melanoma miRNAome by deep sequencing. PloS One, 2010; 5(3): e9685. doi: 10.1371/journal.pone.0009685
35. Eisfeld AK, Marcucci G, Maharry K, Schwind S, Radmacher MD, Nicolet D, et al. miR-3151 interplays with its host gene BAALC and independently affects outcome of patients with cytogenetically normal acute myeloid leukemia. Blood., 2012; 120(2): 249. doi: 10.1182/blood-2012-02-408492 56.
36. Dıaz-BeyaM, Brunet S, Nomdedeu J, Cordeiro A, Tormo M, Escoda L, et al. The expression level of BAALC-associated microRNA miR-3151 is an independent prognostic factor in younger patients with cytogenetic intermediate-risk acute myeloid leukemia. Blood Cancer J., 2015; 5(10): e352. doi: 10.1038/bcj.2015.76
37. Butrym A, Rybka J, BaczynskaD, TukiendorfA, KuliczkowskiK, MazurG. Low expression of microRNA-204 (miR-204) is associated with poor clinical outcome of acute myeloid leukemia (AML) patients. JExp Clin Cancer Res., 2015; 34(1): 68. doi: 10.1186/s13046 015-0184-z
38. Abdelhafiz AS, Elsayed GM, Saber MM, Gameel A, Hamdy N. Low expression of miR-204 is associated with expression of CD34 and poor performance status in denovo AML. Int J Lab Hematol., 2020; 42(3): 263–9. doi: 10.1111/ijlh.13161
39. Hu N, Cheng Z, Pang Y, Zhao H, Chen L, Wang C, et al. High expression of MiR 98 is a good prognostic factor in acute myeloid leukemia patients treated with chemotherapy alone. J Cancer., 2019; 10(1): 178–85. doi: 10.7150/jca.26391