Open Access Research Article

Impact of *IDH* Mutations on DNA Methylation of Acute Myeloid Leukemia Related Genes: A Review Article

Doi: *https://doi.org/10.32007/jfacmedbagdad.6612175*

Duha M. Bayram[1,2] Fadhel M. Lafta[2] Bassam F. Matti[3]

[1]Department of Pharmacology and Toxicology, College of Pharmacy, Mustansiriyah University, Baghdad- Iraq
[2]Department of Biology, College of Science, Baghdad University, Baghdad-Iraq
[3] Haematology Centre, Medical City, Baghdad- Iraq

J Fac Med Baghdad
2024; Vol.66, No. 1
Received: June., 2023
Accepted: Sept., 2023
Published:April .2024

Abstract

Acute myeloid leukemia is one of the deadliest hematologic malignancies that is marked by genetic alterations, abnormal cellular functions and proliferation. Mutations in isocitrate dehydrogenase genes, particularly isocitrate dehydrogenase gene 1 and isocitrate dehydrogenase gene 2, have emerged as recurrent genetic abnormalities in acute myeloid leukemia. These mutations lead to abnormal enzymatic activity, resulting in the accumulation of 2-hydroxyglutarate, which disrupts normal cellular processes including DNA methylation. This review article explores recent findings related to the implication of isocitrate dehydrogenase gene mutations on the acute myeloid leukemia epimethylome and provides evidence to the relationship between these mutations and the pathogenesis, prognosis, and treatment of acute myeloid leukemia. A comprehensive literature search was conducted to identify relevant studies investigating the impact of isocitrate dehydrogenase mutations on altered DNA methylation patterns of acute myeloid leukemia-related genes. The selected studies were reviewed and analyzed to highlight the significance of their findings**.** The review highlights that isocitrate dehydrogenase gene mutations in acute myeloid leukemia are associated with widespread changes in DNA methylation patterns. These alterations primarily affect DNA methylation of acute myeloid leukemia-associated genes, including DNA methyltransferases and ten-eleven translocation proteins. Such epigenetic dysregulation in the DNA methylation modifying genes contributes to global DNA hypermethylation and specific gene hypomethylation leading to abnormal cellular functions and the development of acute myeloid leukemia. The findings of this review support the significant impact of isocitrate dehydrogenase gene mutations on DNA methylation of acute myeloid leukemia-related genes. Understanding the interplay between isocitrate dehydrogenase gene mutations and DNA methylation dysregulation provides insights into acute myeloid leukemia pathogenicity and may have implications for prognostication and targeted therapies.

Keywords: AML; DNA methylation; DNA methyltransferases; IDH; isocitrate dehydrogenase; targeted therapy; TET proteins.

Introduction:

Acute myeloid leukaemia (AML) is a heterogeneous disease defined by the unregulated growth of proliferative progenitor cells that are incapable of terminal differentiation. It is now obvious that numerous genes are often altered in AML (1). However, it is really challenging to identify transformation driver genes within this large number of leukaemia associated disrupted genes. A small fraction of cases can be attributed to identifiable factors, such as previous chemotherapy or exposure to specific chemicals. However, the majority of cases are thought to be a result of genetic alterations, including chromosomal abnormalities and gene mutations (2, 3). Additionally, referring to the disease heterogeneity, individual leukaemia's may include many various mutational profiles, making each AML patient genetically distinct (4-6).

For patients' risk-stratification and selecting the best course of treatment, it's crucial to identify the underlying genetic anomalies (7-9). Recently, the risk classification of AML has been expanded to include three prognostic groups: favourable, moderate, and adverse. These groups take into account both cytogenetic factors and the latest discoveries in molecular subgrouping, in addition to the previously known cytogenetic risk groups. These newly identified molecular subsets exhibit distinct responses to

**Corresponding Author: Duha M. Bayram*
duha.bayram@yahoo.com

standard therapeutic regimens (10-14). As cancer is generally marked by the presence of a wave of genetic abnormalities, identifying the disease's subtype-specific genetic alterations is a difficult task. However, relying on the discovery of next-generation DNA sequencing technologies, the possibility of identifying new recurrent mutations in AML became doable (15). Nevertheless, such approaches offer novel sets of candidate genes, and understanding the underlying genetic and epigenetic pathways of such alterations requires systematic validation through conducting of functional studies (16). So, this review article seeks to explore how IDH mutations affect the DNA methylation patterns of genes linked to acute myeloid leukemia (AML). It aims to provide a comprehensive analysis of the impact of these mutations on epigenetic changes, specifically focusing on DNA methylation, in the development of AML. To structure this review, we will begin with an introduction that provides an overview on DNA methylation and IDH mutations. Following that, we will delve into the molecular mechanisms by which IDH mutations affect DNA methylation, emphasizing their role in reshaping the epigenetic landscape of AML-related genes. Next, we will explore the clinical significance and prognostic implications of IDH mutations in AML patients, including their potential as therapeutic targets. Finally, we will conclude the review by summarizing key between IDH mutations and DNA methylation in the context of AML.

Epigenetic regulation of cellular transcription activity via DNA methylation

The epigenetic modifications including the process of DNA methylation (in addition to histone modifications), which predominantly takes place in CpG islands near the 5′ promoter region of almost 60% of human genes, is the most thoroughly researched one (17, 18). Such epigenetic marks demonstrate a crucial role in both normal development and health problems. These include their impact on embryonic development, inactivation of the X chromosome, epigenetic reprogramming, genomic imprinting, and lineage specification. DNA hypermethylation has been linked to gene silencing by the covalent attachment of methyl groups to the 5 positions of the cytosine pyrimidine ring, which results in suppressive gene expression (19-21).

In various cell types, the balanced regulation of genome methylation and demethylation is a dynamic process of gene expression. Three DNA methyltransferases (DNMTs) carry out the catalysis of DNA methylation. DNMT1 plays a crucial role in maintaining the DNA methylation state (22, 23). DNMT3a and DNMT3b, known as "de novo" methyltransferases, work together to establish and maintain precise DNA methylation patterns across the genome (24). Conversely, DNA demethylation is a reversible process that restores gene expression silenced by DNMTs. The activity of demethylation is attributed to members of the ten-eleven translocation methylcytosine dioxygenase (TET) family, including TET1, TET2, and TET3 (25-28).

Also, numerous other proteins included in cellular metabolic processes contribute to chromatin remodeling and gene regulation as a result of the interconnection between metabolism and epigenetics by creating substrates or co-factors utilized by epigenetic writers that are able to add a different chemical modification to histones or DNA (29, 30). One example of epigenetic modifiers is the isocitrate dehydrogenase (IDH) enzymes. These enzymes convert isocitrate to α-ketoglutarate, either in the mitochondrion during the tricarboxylic acid (TCA) cycle, specifically by IDH1, or in the cytoplasm by IDH2. This process leads to the generation of α-ketoglutarate, which serves as a co-factor for various α-ketoglutarate dependent dioxygenases. These include crucial enzymes such as the DNA demethylases mediated by ten-eleven translocation (TET) family and the histone demethylases in the Jumonji family (31, 32).

Mutant genes are frequently seen in cancer which directly leads to aberrant normal DNA methylation controls and thus generate dysregulation of gene expression. A number of DNA methylation modifier genes were reported in AML that may act as DNA methyl-transfer or demethylation enzymes (31, 33). However, the top seven most frequent DNA methylation-related genes' mutations in AML are illustrated in Figure (1). In the case of acute myeloid leukemia, DNMT3A mutations were highly documented over the world, followed by IDH1/2 and TET2 mutation, while the ratio was equivalent in the remaining genes.

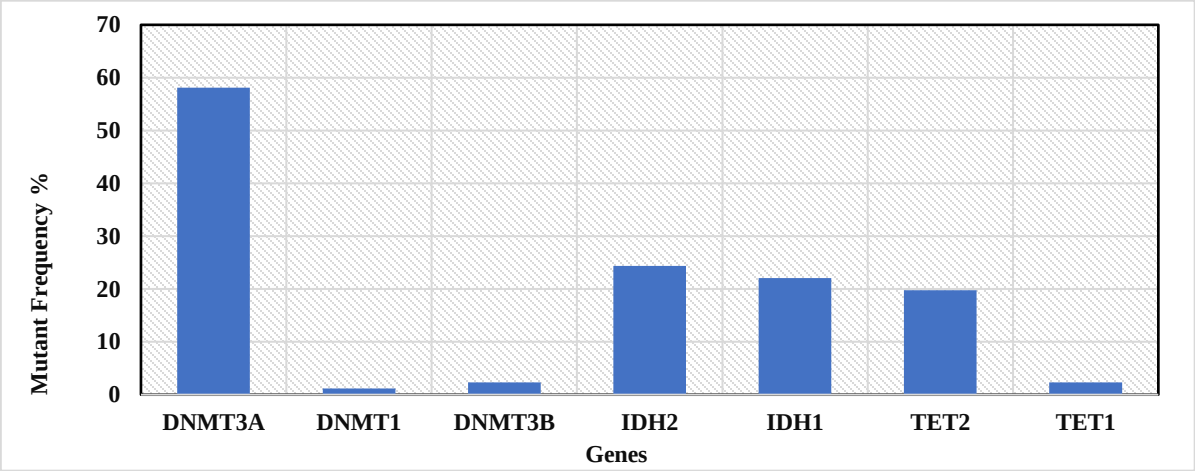
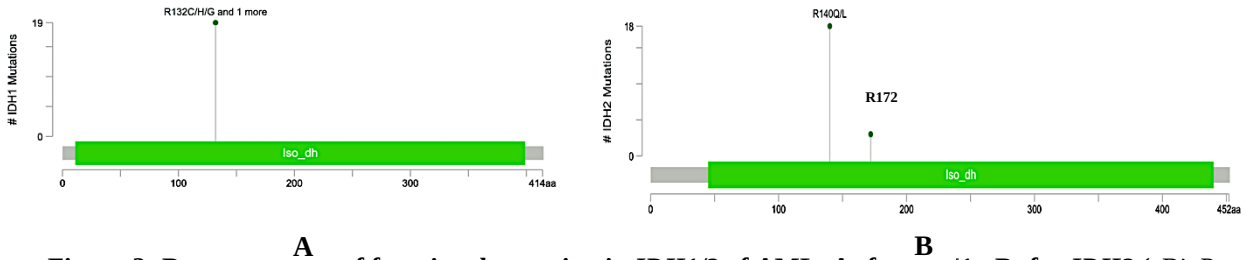


Figure-1: Percentage of samples with one or more mutations in DNA methylation-related genes in AML. Clinic genomic data were adopted from the cBioPortal database.

Role of IDH1/2 as epigenetic-related mutations genes in AML:

IDHs gene mutations have been extensively investigated in solid and liquid tumors since these mutations were originally reported in glioblastoma. It has been then found in a variety of tumor forms, including sinonasal undifferentiated carcinoma, chondrosarcomas, prostate cancer, and acute myeloid leukemia (34, 35).

AML patients have been reported to exhibit acquired mutations at varying rates. For instance, a study conducted by (34) found that IDH mutations were present in 16% of AML patients, in which IDH1 and IDH2 mutations were detected in 7.6% and 8.7% of patients, respectively. These mutations are believed to arise from heterozygous mutations occurring in substrate binding residues, leading to alterations in the amino acid arginine at exon 4 of the IDH1/2 genes (specifically, at codon R132 of IDH1 and codons R140 and R172 of IDH2) (Fig 2). The majority of IDH1 mutations were predicted to result in various substitutions of arginine at position 132, while IDH2 mutations were primarily missense mutations causing amino acid changes at positions p.R140 and p.R172 (Table 1 and Fig 3) (36-40).



A **B**

Figure-2: Recurrent gain of functional mutation in *IDH1/2* of AML, A: for *IDH1* ; B: for *IDH2* (cBioPortal for Cancer Genomics**).**

IDH enzymes have been involved in several cellular metabolic and epigenetic processes. About 20% of acute myeloid leukaemia have *IDH1* or *IDH2* mutations, which cause amino acid alterations in conserved residues, resulting in neomorphic enzymatic activity, and the generation of rare metabolite 2-HG (2-hydroxyglutarate) which accumulated in cells and serve as oncometabolite. DNA hypermethylation, inappropriate cell proliferation or differentiation, and dysregulated gene expression are the results of such IDH enzyme deregulation.

According to the existing data, it seems that IDH mutations have a role in the development of cancer. These mutations decrease the affinity of the enzymes for their substrates and acquire a new function, leading to the conversion of alpha-ketoglutarate (a-KG), a key mediator in the Krebs cycle, into 2-hydroxyglutarate (2-HG), which has a significant impact on pathophysiology. The accumulation of 2-HG resulting

from these mutations contributes to cancer development because it structurally resembles a-KG and can interfere with the function of enzymes that rely on a-KG as a substrate, such as lysine demethylases and TET proteins. Specifically, the catalytic activity of the TET2 enzyme, a member of the a-KG-dependent dioxygenases family, is inhibited by the presence of R-2HG, which is produced as a result of gain-of-function IDH1/2 mutations (Fig. 4) (41, 42).

In a previous study, it was observed that the levels of 2-hydroxyglutarate (2-HG) are notably increased in the blood serum of AML patients with IDH1/2 mutations. Therefore, the presence of elevated 2-HG levels can be used as an indicator to predict the presence of IDH1/2 mutations and the clinical prognosis of AML (43, 44). The presence of 2-hydroxyglutarate (2-HG) alone is capable of facilitating the transformation of hematopoietic cells, and this impact can be reversed by removing the oncometabolite (45). Furthermore, mutant IDH1/2 promotes an excessive methylation pattern in hematopoietic cells, leading to abnormalities in their differentiation process. As a result, the suppression of tumor suppressor genes through DNA hypermethylation is anticipated to generate a greater number of progenitor cells with an extended capacity for proliferation (46, 47).

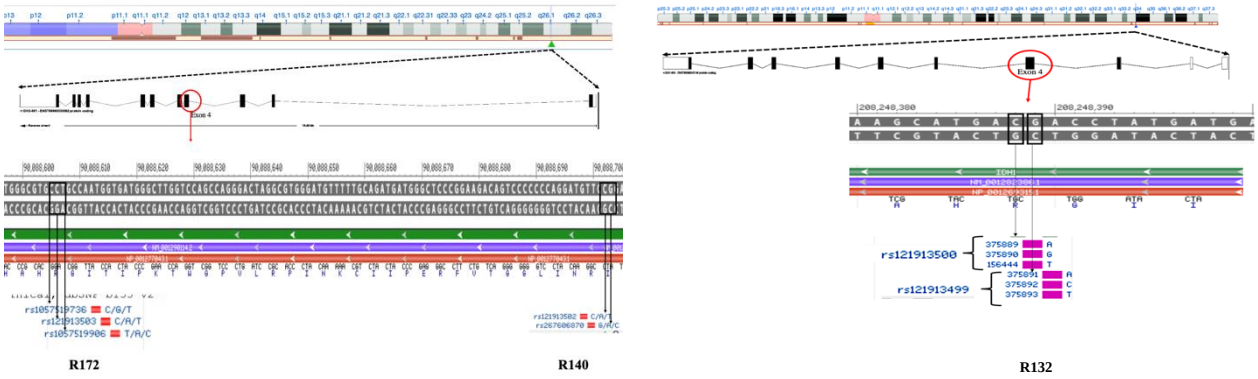


Figure-4: *IDH* genes map adapted from NCBI illustrates the locations of pathogenic mutations (left: *IDH1*, right: *IDH2*).

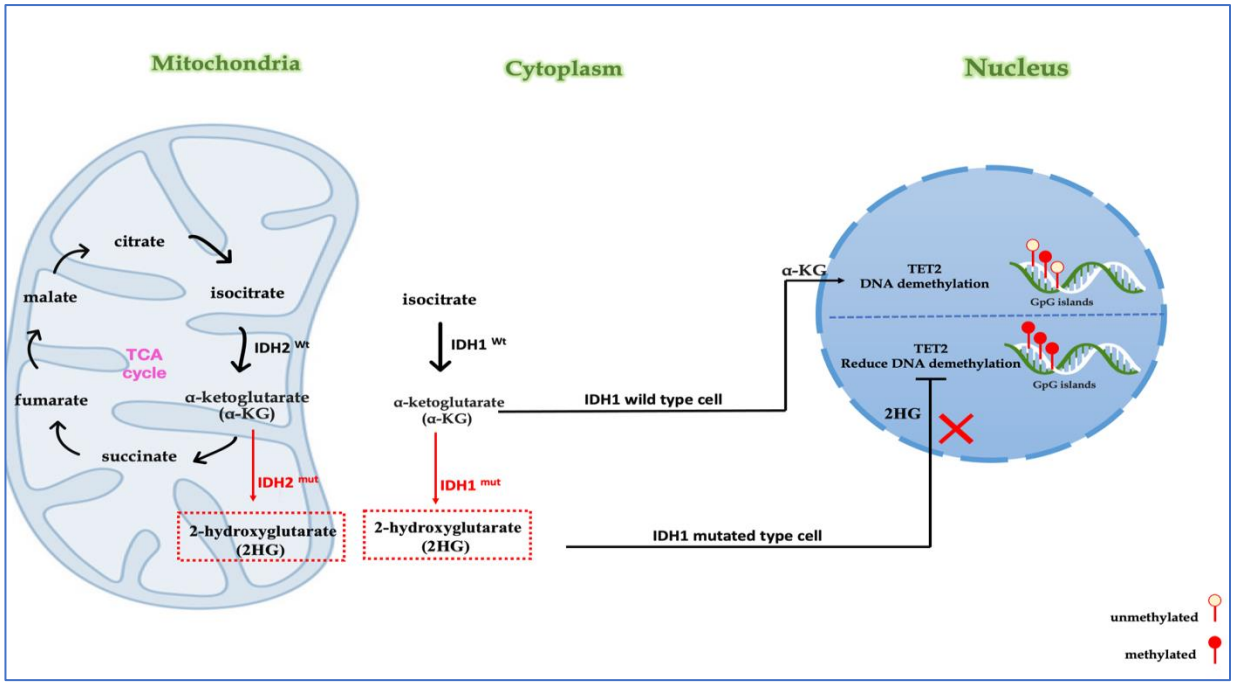


Figure-4 Mutant IDH1 and IDH2 enhance production of 2HG from a-Ketoglutarate (aKG).

Table-1: List of the most frequently occurring variation in *IDH1/2* of AML recorded in NCBI

Variation (*Location)*	Protein change	Condition	SNP ID	Type
IDH1				
c.395G>C **c.395G>T** ***c.395G>A*** **(*GRCh38:* Chr2:208248388)**	R132P (p.Arg132Pro) R132L (p.Arg132Leu) R132H (p.Arg132His)	Pathogenic (Oct 2, 2014) Pathogenic/Likely pathogenic (May 31, 2016) Pathogenic (May 9, 2022)	rs121913499	Missense
c.394C>A **c.394C>G** **c.394C>T** **(*GRCh38:* Chr2:208248389)**	R132S (p.Arg132Ser) R132G (p.Arg132Gly) R132C (p.Arg132Cys)	Pathogenic/Likely pathogenic (May 31, 2016) Pathogenic/Likely pathogenic (May 31, 2016) Pathogenic/Likely pathogenic (May 9, 2022)	rs121913499	Missense
IDH2				
c.516G>C ***(GRCh38:*** **Chr15:90088605)**	R172S (p.Arg172Ser)	Pathogenic; risk factor (Oct 2, 2014)	rs1057519736	Missense
c.515G>A **c.515G>T** ***(GRCh38:*** **Chr15:90088606)**	R172K, (p.Arg172Lys) R172M (p.Arg172Met)	Pathogenic/Likely pathogenic; risk factor (May 31, 2016)	rs121913503	Missense
c.514A>G **c.514A>T** ***(GRCh38:*** **Chr15:90088607)**	R172G (p.Arg172Gly) R172W (p.Arg172Trp)	Likely pathogenic (May 31, 2016) ; Likely pathogenic risk factor (May 31, 2016)	rs1057519906	Missense
c.419G>T **c.419G>A** ***(GRCh38:*** **Chr15:90088702)**	R140L (p.Arg140Leu) R140Q (p.Arg140Gln)	Pathogenic/Likely pathogenic (May 31, 2016) Pathogenic/Likely pathogenic (Oct 2, 2021)	rs121913502	Missense
c.418C>T ***(GRCh38:*** **Chr15:90088703)**	R140W (p.Arg140Trp)	Uncertain significance (Dec 3, 2021)	rs267606870	Missense

Prognostic significance of IDH mutations

Many researchers have attempted to establish the potential link between the occurrence of *IDH* mutations and the disease's progression or prognosis of AML aiming to explore their utility as drug targets for treating patients on the bases of potential personalized medicine (48). The arrangement of excessively methylated genes in AML cases with IDH1/IDH2 mutations is similar to the pattern observed in TET2-loss-of-function mutations. These changes in the epigenetic profile result in impaired development of myeloid cells, likely due to the repression of certain transcription factors. Compared to individuals without these mutations, patients with IDH-mutated AML are frequently older and exhibit a reduced count of white blood cells (49-51).

Although a recent study (52) found that a mutant-NPM1/wild-FLT3 genotype in conjunction with an *IDH1* or *IDH2* mutation confers a very good prognosis factor. According to other research, a normal AML karyotype carries a poor prognosis when *IDH1*

mutations are present. These variations may be caused by the specific location of the mutation in the *IDH* gene, which is likely to have an impact on how the disease will progress, or by the varied responses to different treatment options (52).

Recent research indicates that IDH mutations alone are not sufficient to predict prognosis accurately, and their occurrence is influenced by age. The survival rates of patients with wild-type IDH and those with IDH mutations do not show significant differences. However, for patients with IDH mutations, having dual mutations involving both IDH and NPM1 significantly improves the prognosis for 5-year event-free survival for AML patients compared to patients with IDH-mutated/NPM1 wild-type. The positive predictive impact of dual IDH/NPM1 mutation status varies with age, particularly in younger and middle-aged patients. Moreover, the presence of a triple mutation (IDH/NPM1/DNMT3A) is associated with a poorer prognosis in the subgroup of middle-aged patients when compared to those with dual IDH/NPM1 mutations (with wild-type DNMT3A) (53).

IDH inhibitors (IDH-i) : Due to the abundance of research on IDH mutations and their effect on the development of AML, several inhibitors have been developed for the mutant *IDH1*/*IDH2* to reduce the deleterious effect of these mutant genes that cause abnormal maturation of leukocyte, leads to leukaemia. Ivosidenib and enasidenib, two of the IDH-i targets, it works by inhibiting the IDH1 and IDH2 proteins respectively. This inhibition permits what would otherwise be leukaemic white blood cells to grow and differentiate normally, lowering the number of immature blasts and raising the percentage of mature myeloblasts (52, 54, 55).

IDH inhibitor and relapsed/ refractory AML: Patients with refractory AML had considerably greater levels of metabolic IDH1 and variability in the gene expression related to epigenetic regulation. such epigenetic change seems to have a significant impact on developing refractory AML and may be helpful in predicting the prognosis of AML (56, 57).

Recently, IDH inhibitors have shown a significant influence in improving the clinical outcomes of AML patients (58-60). As a result, the IDH2 and IDH1 inhibitor drugs enasidenib and ivosidenib have been authorized for the treatment of adult AML that has relapsed or is resistant to conventional therapy. Although effective and reliable, IDH inhibitor monotherapy for relapsed/ refractory **(**R/R) AML has drawbacks, such as primary or acquired resistance (61). So, for the treatment of R/R AML or newly diagnosed AML, many clinical trials seek to find the patients' response to mutation inhibitors (especially IDH inhibitors) in combination with hypomethylating drugs or conventional chemotherapy as well as in the after hematopoietic stem cell transplantation as maintenance therapy (62-67).

Conclusions

This review drew attention to the significance of IDH1/2 mutations as a key valid marker to improve the clinical outcome of AML patients via the development of targeted therapy based on IDH1/2 inhibitors. The wide spectrum of IDH1 and IDH2 gene mutations in AML implies the possibility of utilizing such knowledge in stratifying AML patients into different prognostic categories that would modify the treatment intensification hoping to minimize the short and long terms side effects associated with conventional therapeutic regimens.

Conflicts of Interest: None.

Authors' declaration: We confirm that all the Tables/Figures in the manuscript are original creations by the authors.

Authors Declaration:

We confirm that all the Figures and Tables in the manuscript belong to the current study. Besides, the Figures and images, which do not belong to the current study, have been given permission for re-publication attached to the manuscript. Authors sign on ethical consideration's approval-

Ethical Clearance: The project was approved by the local ethical committee in (the Biology Department, College of Science, University of Baghdad, under reference code (Ref. CSEC/0922/0082).

Authors' Contribution:

Study conception & design: (Duha M. Bayram,' Fadhel M. Lafta, Bassam F. Matti). Literature search: (Duha M. Bayram,' Fadhel M. Lafta, Bassam F. Matti). Data acquisition: (Duha M. Bayram,' Fadhel M. Lafta, Bassam F. Matti). Data analysis & interpretation: (Duha M. Bayram,' Fadhel M. Lafta, Bassam F. Matti). Manuscript preparation: (Duha M. Bayram,' Fadhel M. Lafta, Bassam F. Matti). Manuscript editing & review: (Duha M. Bayram,' Fadhel M. Lafta, Bassam F. Matti).

References

1. Hamad HM, Shabeeb ZA, Awad MM. Expressions of CD274 (PD-L1) and CD47 rReceptors on the sSurface of bBlast cCells in AML pPatients. IJS. 2020; 63(6), 2373–2387. Available from: https://doi.org/10.24996/ijs.2022.63.6.6

2. Obeagu EI, Babar Q. Acute Myeloid Leukaemia (AML): The Good, the Bad, and the Ugly. Int J Curr Res Med Sci. 2021;7(7):29-41. Available from: 10.22192/ijcrms.2021.07.07.004

3. Heimbruch KE, Meyer AE, Agrawal P, Viny AD, Rao S. A cohesive look at leukemogenesis: The cohesin complex and other driving mutations in AML.

Neoplasia. 2021;23(3):337-47. DOI: 10.1016/j.neo.2021.01.003
4. Grimwade D, Ivey A, Huntly BJ. Molecular landscape of acute myeloid leukemia in younger adults and its clinical relevance. Blood, The Journal of the American Society of Hematology. 2016;127(1):29-41. DOI: 10.1182/blood-2015-07-604496
5. Stelmach P, Trumpp A. Leukemic stem cells and therapy resistance in acute myeloid leukemia. Haematologica. 2023;108(2):353. Available from: https://doi.org/10.3324/haematol.2022.280800
6. Al-Mudallel SS, Dhahi MA. Detection of FLT3-ITDMutation in Twenty ChildwithAcuteMyeloidLeukemia in One Iraqi Teaching Hospital. Journal of the Faculty of Medicine Baghdad. 2012;54(2):138-41. Available from: https://doi.org/10.24996/ijs.2022.63.6.6
7. Zhang N, Chen Y, Lou S, Shen Y, Deng J. A six-gene-based prognostic model predicts complete remission and overall survival in childhood acute myeloid leukemia. Onco Targets Ther. 2019;12:6591.DOI: 10.2147/OTT.S218928
8. Elgarten CW, Aplenc R. Pediatric acute myeloid leukemia: updates on biology, risk stratification, and therapy. Curr Opin Pediatr. 2020;32(1):57-66. Available from: 10.1097/MOP.0000000000000855
9. AL-Khalissi KA. Experience with treatment of fifty eight Iraqi patients with acute myeloid leukemia. Journal of the Faculty of Medicine Baghdad. 2013;55(4):290-5. Available from: https://doi.org/10.32007/jfacmedbagdad.554566 .
10. Pelcovits A, Niroula R. Acute myeloid leukemia: a review. Rhode Island Medical Journal. 2020;103(3):38-40. PMID: 32236160.
11. Walker CJ, Mrózek K, Ozer HG, Nicolet D, Kohlschmidt J, Papaioannou D, et al. Gene expression signature predicts relapse in adult patients with cytogenetically normal acute myeloid leukemia. Blood advances. 2021;5(5):1474-82. Available from: 10.1182/bloodadvances.2020003727
12. Herold T, Rothenberg-Thurley M, Grunwald VV, Janke H, Goerlich D, Sauerland MC, et al. Validation and refinement of the revised 2017 European LeukemiaNet genetic risk stratification of acute myeloid leukemia. Leukemia. 2020;34(12):3161-72. Available from: 10.1038/s41375-020-0806-0
13. Rausch C, Rothenberg-Thurley M, Dufour A, Schneider S, Gittinger H, Sauerland C, et al. Validation and refinement of the 2022 European LeukemiaNet genetic risk stratification of acute myeloid leukemia. Leukemia. 2023:1-11. DOI: 10.1038/s41375-023-01884-2
14. Mohammed SK, AL-Faisal AHM. Study of Chromosomal Aberrations and Micronucleus Formation in Some Iraqi Patients infected with Acute Myeloid Leukemia (AML). Iraqi journal of biotechnology. 2014;13(1). Available from: https://jige.uobaghdad.edu.iq/index.php/IJB/article/view/264
15. Garcia-Heras J. Optical Genome Mapping: A Revolutionary Tool for "Next Generation Cytogenomics Analysis" with a Broad Range of Diagnostic Applications in Human Diseases. Journal of the Association of Genetic Technologists. 2021;47(4). PMID: 34897113
16. Celton M, Forest A, Gosse G, Lemieux S, Hebert J, Sauvageau G, et al. Epigenetic regulation of GATA2 and its impact on normal karyotype acute myeloid leukemia. Leukemia. 2014;28(8):1617-26. Available from: https://doi.org/10.1038/leu.2014.67.
17. Sandoval J, Heyn H, Moran S, Serra-Musach J, Pujana MA, Bibikova M, et al. Validation of a DNA methylation microarray for 450,000 CpG sites in the human genome. Epigenetics. 2011;6(6):692-702. DOI: 10.4161/epi.6.6.16196
18. Cheng Y, He C, Wang M, Ma X, Mo F, Yang S, et al. Targeting epigenetic regulators for cancer therapy: mechanisms and advances in clinical trials. Signal transduction and targeted therapy. 2019;4(1):62. Available from: https://doi.org/10.3390/ijms22052305.
19. Lu Y, Chan Y-T, Tan H-Y, Li S, Wang N, Feng Y. Epigenetic regulation in human cancer: the potential role of epi-drug in cancer therapy. Mol Cancer. 2020;19(1):1-16. Available from: https://doi.org/10.1186/s12943-020-01197-3
20. Pulikkottil AJ, Bamezai S, Ammer T, Mohr F, Feder K, Vegi NM, et al. TET3 promotes AML growth and epigenetically regulates glucose metabolism and leukemic stem cell associated pathways. Leukemia. 2022;36(2):416-25. DOI: 10.1038/s41375-021-01390-3
21. Zhang L, Lu Q, Chang C. Epigenetics in health and disease. Epigenetics in allergy and autoimmunity. 2020:3-55. DOI: 10.1007/978-981-15-3449-2_1
22. Ren W, Fan H, Grimm SA, Guo Y, Kim JJ, Yin J, et al. Direct readout of heterochromatic H3K9me3 regulates DNMT1-mediated maintenance DNA methylation. Proceedings of the National Academy of Sciences. 2020;117(31):18439-47. DOI: 10.1073/pnas.2009316117
23. Heredia-Mendez AJ, Sánchez-Sánchez G, López-Camarillo C. Reprogramming of the Genome-Wide DNA Methylation Landscape in Three-Dimensional Cancer Cell Cultures. Cancers (Basel). 2023;15(7):1991. DOI: 10.3390/cancers15071991
24. Gao L, Emperle M, Guo Y, Grimm SA, Ren W, Adam S, et al. Comprehensive structure-function characterization of DNMT3B and DNMT3A reveals distinctive de novo DNA methylation mechanisms. Nature communications. 2020;11(1):1-14. Available from: https://doi.org/10.1038/s41467-020-17109-4
25. Shekhawat J, Gauba K, Gupta S, Choudhury B, Purohit P, Sharma P, et al. Ten–eleven translocase: key regulator of the methylation landscape in cancer. J

Cancer Res Clin Oncol. 2021;147(7):1869-79. DOI: 10.1007/s00432-021-03641-3
26. Zeng Y. Regulation of de novo and Maintenance DNA Methylation by DNMT3A and DNMT3B. 2023. Available from: https://digitalcommons.library.tmc.edu/utgsbs_dissertations/1264/
27. Joshi K, Liu S, Breslin SJ P, Zhang J. Mechanisms that regulate the activities of TET proteins. Cell Mol Life Sci. 2022;79(7):363. DOI: 10.1007/s00018-022-04396-x
28. Jiang S. Tet2 at the interface between cancer and immunity. Communications biology. 2020;3(1):667. Available from: https://doi.org/10.1038/s42003-020-0139.
29. Wellen KE, Hatzivassiliou G, Sachdeva UM, Bui TV, Cross JR, Thompson CB. ATP-citrate lyase links cellular metabolism to histone acetylation. Science. 2009;324(5930):1076-80.
DOI: 10.1126/science.1164097
30. Nicholson TB, Veland N, Chen T. Writers, readers, and erasers of epigenetic marks. Epigenetic Cancer Therapy: Elsevier; 2015. p. 31-66. Available from: 10.1016/B978-0-12-800206-3.00003-3
31. Raineri S, Mellor J. IDH1: linking metabolism and epigenetics. Frontiers in genetics. 2018:493. Available from: https://doi.org/10.3389/fgene.2018.00493
32. Nikolaev A, Fiveash JB, Yang ES. Combined targeting of mutant p53 and Jumonji family histone demethylase augments therapeutic efficacy of radiation in H3K27M DIPG. Int J Mol Sci. 2020;21(2):490. DOI: 10.3390/ijms21020490
33. Lee C-J, Ahn H, Jeong D, Pak M, Moon JH, Kim S. Impact of mutations in DNA methylation modification genes on genome-wide methylation landscapes and downstream gene activations in pan-cancer. BMC Med Genomics. 2020;13:1-14. Available from: https://doi.org/10.1186/s12920-020-0659-4
34. Pelosi E, Castelli G, Testa U. Isocitrate dehydrogenase mutations in human cancers: physiopathologic mechanisms and therapeutic targeting. Journal of Exploratory Research in Pharmacology. 2016;1(1):20-34. DOI: 10.14218/JERP.2016.00019
35. Senhaji N, Squalli Houssaini A, Lamrabet S, Louati S, Bennis S. Molecular and circulating biomarkers in patients with glioblastoma. Int J Mol Sci. 2022;23(13):7474. Available from: https://doi.org/10.3390/ijms23137474
36. Willander K, Falk IJ, Chaireti R, Paul E, Hermansson M, Gréen H, et al. Mutations in the isocitrate dehydrogenase 2 gene and IDH1 SNP 105C> T have a prognostic value in acute myeloid leukemia. Biomarker research. 2014;2(1):1-9. Available from: https://doi.org/10.1186/2050-7771-2-18
37. Alkhatabi H, Bin Saddeq HA, Alyamani L, Shinawi T, Yasin EB, Alserihi R, et al. Investigation of Isocitrate Dehydrogenase 1 and 2 Mutations in Acute Leukemia Patients in Saudi Arabia. Genes. 2021;12(12):1963. Available from: https://doi.org/10.3390/genes12121963.
38. Cumbo C, Minervini CF, Orsini P, Anelli L, Zagaria A, Minervini A, et al. Nanopore targeted sequencing for rapid gene mutations detection in acute myeloid leukemia. Genes. 2019;10(12):1026. PMID: 31835432
39. Rausch C, Rothenberg-Thurley M, Buerger SA, Tschuri S, Dufour A, Neusser M, et al. Double drop-off droplet digital pcr: A novel, versatile tool for mutation screening and residual disease monitoring in acute myeloid leukemia using cellular or cell-free DNA. The Journal of Molecular Diagnostics. 2021;23(8):975-85. DOI: 10.1016/j.jmoldx.2021.05.001
40. Beck RC, Kim AS, Goswami RS, Weinberg OK, Yeung CC, Ewalt MD. Molecular/Cytogenetic Education for Hematopathology Fellows: A Recommended Curriculum From the Society for Hematopathology and the Association for Molecular Pathology. Am J Clin Pathol. 2020;154(2):149-77. Available from: https://doi.org/10.1093/ajcp/aqaa038.
41. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2009;462(7274):739-44. Available from: https://doi.org/10.1038/nature08617
42. Heiblig M. Les mutations d'IDH2 dans la leucémie aigue myéloïde confèrent une sensibilité spécifique à l'inhibition du métabolisme des acides aminés branchés (BCAA): Université Paris-Saclay; 2022. Available from: https://theses.hal.science/tel-04108390/document
43. DiNardo CD, Propert KJ, Loren AW, Paietta E, Sun Z, Levine RL, et al. Serum 2-hydroxyglutarate levels predict isocitrate dehydrogenase mutations and clinical outcome in acute myeloid leukemia. Blood, The Journal of the American Society of Hematology. 2013;121(24):4917-24. DOI: 10.1182/blood-2013-03-493197
44. Pang H, Jia W, Hu Z. Emerging applications of metabolomics in clinical pharmacology. Clin Pharmacol Ther. 2019;106(3):544-56. DOI: 10.1002/cpt.1538
45. Losman J-A, Looper RE, Koivunen P, Lee S, Schneider RK, McMahon C, et al. (R)-2-hydroxyglutarate is sufficient to promote leukemogenesis and its effects are reversible. Science. 2013;339(6127):1621-5.
DOI: 10.1126/science.1231677
46. Figueroa ME, Abdel-Wahab O, Lu C, Ward PS, Patel J, Shih A, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic

differentiation. Cancer Cell. 2010;18(6):553-67. DOI: 10.1016/j.ccr.2010.11.015
47. Zhou H, Zhang Q, Huang W, He C, Zhou C, Zhou J, et al. Epigenetic silencing of ZCCHC10 by the lncRNA SNHG1 promotes progression and venetoclax resistance of acute myeloid leukemia. Int J Oncol. 2023;62(5):1-11. DOI: 10.3892/ijo.2023.5512
48. Angelakas A, Lamarca A, Hubner RA, McNamara MG, Valle JW. Ivosidenib: An investigational drug for the treatment of biliary tract cancers. Expert Opinion on Investigational Drugs. 2021;30(4):301-7. Available from: https://doi.org/10.1080/13543784.2021.1900115.
49. Sun Y, Chen B-R, Deshpande A. Epigenetic regulators in the development, maintenance, and therapeutic targeting of acute myeloid leukemia. Front Oncol. 2018;8:41. Available from: https://doi.org/10.3389/fonc.2018.00041
50. Davis AR, Canady BC, Aggarwal N, Bailey NG. Clinicopathologic Features of IDH2 R172–Mutated Myeloid Neoplasms. Am J Clin Pathol. 2023:aqad019. DOI: 10.1093/ajcp/aqad019
51. Bill M, Jentzsch M, Bischof L, Kohlschmidt J, Grimm J, Schmalbrock LK, et al. Impact of IDH1 and IDH2 mutation detection at diagnosis and in remission in patients with AML receiving allogeneic transplantation. Blood Advances. 2023;7(3):436-44. Available from: https://doi.org/10.1002/onco.13656.
52. Abou Dalle I, DiNardo CD. The role of enasidenib in the treatment of mutant IDH2 acute myeloid leukemia. Therapeutic advances in hematology. 2018;9(7):163-73. Available from: https://doi.org/10.1177/2040620718777467.
53. Beat A. Study Offers Insights on Prognostic Significance of IDH Mutations Across Age Groups in AML. The Oncologist. 2020;26:S13–S4. Available from: https://doi.org/10.1002/onco.13656.
54. Myers RA, Wirth S, Williams S, Kiel PJ. Enasidenib: an oral IDH2 inhibitor for the treatment of acute myeloid leukemia. Journal of the advanced practitioner in oncology. 2018;9(4):435. PMID: 30719396
55. Aiman W, Ali MA, Basit MA, Omar Z, Suleman M, Hassan M, et al. Efficacy and Tolerability of Isocitrate Dehydrogenase Inhibitors in Patients with Acute Myeloid Leukemia: A Systematic Review of Clinical Trials. Leuk Res. 2023:107077. Available from: https://doi.org/10.1016/j.leukres.2023.107077.
56. McDevitt MA, editor Clinical applications of epigenetic markers and epigenetic profiling in myeloid malignancies. Semin Oncol; 2012: Elsevier.
57. Montalban-Bravo G, DiNardo CD. The role of IDH mutations in acute myeloid leukemia. Future Oncology. 2018;14(10):979-93. DOI: 10.2217/fon-2017-0523
58. Liu X, Gong Y. Isocitrate dehydrogenase inhibitors in acute myeloid leukemia. Biomarker research. 2019;7(1):1-8. DOI: https://doi.org/10.1186/s40364-019-0173-z
59. Wang J, Tomlinson B, Lazarus HM. Update on Small Molecule Targeted Therapies for Acute Myeloid Leukemia. Curr Treat Options Oncol. 2023:1-32. DOI: 10.1007/s11864-023-01090-3
60. Venugopal S, Watts JM. Olutasidenib: from bench to bedside. Blood Advances. 2023:bloodadvances. 2023; 009854. DOI: 10.1182/bloodadvances.2023009854
61. Leotta S, Condorelli A, Sciortino R, Milone GA, Bellofiore C, Garibaldi B, et al. Prevention and treatment of acute myeloid leukemia relapse after hematopoietic stem cell transplantation: the state of the art and future perspectives. Journal of Clinical Medicine. 2022;11(1):253. DOI: 10.3390/jcm11010253
62. Testa U, Pelosi E, Castelli G. Cancer stem cell targeted therapies. Ann Ist Super Sanita. 2020;56(3):336-50. DOI: 10.4415/ANN_20_03_12
63. Thol F, Ganser A. Treatment of relapsed acute myeloid leukemia. Curr Treat Options Oncol. 2020;21(8):1-11. DOI: 10.1007/s11864-020-00765-5
64. Guinn B, Schuler PJ, Schrezenmeier H, Hofmann S, Weiss J, Bulach C, et al. A combination of the immunotherapeutic drug anti-programmed death 1 with lenalidomide enhances specific T cell immune responses against acute myeloid leukemia cells. Int J Mol Sci. 2023;24(11):9285. DOI: 10.3390/ijms24119285
65. AL-KZAYER, Lika'a Fasih Y., et al. Analysis of KRAS and NRAS gene mutations in Arab Asian children with acute leukemia: high frequency of RAS mutations in acute lymphoblastic leukemia. Pediatric blood & cancer. 2015, 62.12: 2157-2161.
66. Bashi MA, Ad'hiah AH. Interleukin-37 gene expression is down-regulated in patients with acute myeloid leukemia and shown to be affected by CD14 and HLA-DR immunophenotypes. Cytokine. 2023 Nov;171:156368. doi: 10.1016/j.cyto.2023.156368. Epub 2023 Sep 15. PMID: 37716188.
67. Bashi MA, Ad'hiah AH. Molecular landscape of the interleukin-40 encoding gene, C17orf99, in patients with acute myeloid leukemia. Gene. 2024 Apr 30;904:148214. doi: 10.1016/j.gene.2024.148214. Epub 2024 Jan 28. PMID: 38286266.

How to Cite this Article:
Impact of IDH mutations on DNA methylation of acute myeloid leukemia related genes: A review . JFacMedBagdad [Internet]. [cited 2024 Mar. 23];66(1). Available from: https://iqjmc.uobaghdad.edu.iq/index.php/19JFacMedBaghdad36/article/view/2175

تأثير الطفرات في الـIDH على مثيلة الدنا للجينات المرتبطة بسرطان الدم النخاعي الحاد: مقالة مراجعة

ضحى مهند بيرم/ فرع الادوية والسموم ، كلية الصيدلة ، الجامعة المستنصرية ، بغداد ، العراق و
قسم علوم الحياة ، كلية العلوم ، جامعة بغداد ، بغداد ، العراق
فاضل محمد لفتة/ قسم علوم الحياة ، كلية العلوم ، جامعة بغداد ، بغداد ، العراق
،بسام فرنسيس متي/ مركز أمراض الدم، مدينة الطب ، بغداد ، العراق

الخلاصة
ابيضاض الدم النخاعي الحاد هو أحد أكثر الأورام الدموية الخبيثة فتكًا و تتميز بوظائف خلوية غير طبيعية وتغيرات جينية. و تبين ان الطفرات في جينات نازعة هيدروجين إيزوسيترات وخاصة جين نازعة هيدروجين إيزوسيترات *1* و جين نازعة هيدروجين إيزوسيترات *2* ، على أنها تشوهات وراثية متكررة في مرضى ابيضاض الدم النخاعي الحاد. و تؤدي هذه الطفرات إلى نشاط إنزيمي غير طبيعي، مما يؤدي إلى تراكم 2-هيدروكسي جلوتارات و الذي بدوره يعطل العمليات الخلوية الطبيعية بما في ذلك مثيلة الحمض النووي. تهدف مقالة المراجعة هذه إلى استعراض الطفرات الجينية المسجلة لجين نازعة هيدروجين إيزوسيترات , التحقق من العلاقة بين تلك الطفرات والتغييرات في أنماط مثيلة الحمض النووي، وآثارها على التسبب في الإصابة بابيضاض الدم النخاعي الحاد والتنبؤ به وعلاجه. تم إجراء بحث شامل في الأدبيات العلمية لتحديد الدراسات ذات الصلة التي تبحث في تأثير الطفرات لجين نازعة هيدروجين إيزوسيترات على الجينات المرتبطة بمثيل الحمض النووي في المرضى الذين يعانون من ابيضاض الدم . وتمت مراجعة الدراسات المختارة وتحليلها لغرض الوصول الى المعلومات والمعرفة الحالية حول هذا الموضوع. سلطت هذه المقالة الضوء على أن طفرات جين نازعة هيدروجين إيزوسيترات في مرضى ابيضاض الدم النخاعي الحاد مرتبطة بتغيرات واسعة النطاق في أنماط مثيلة الحمض النووي. تؤثر هذه التغييرات في المقام الأول على الجينات المرتبطة بإضافة مجموعة المثيل الى الحمض النووي، بما في ذلك DNA methyltransferases وبروتينات ten-eleven translocation . بالتالي يؤدي خلل تنظيم مثيلة الحمض النووي إلى فرط مثيل الحمض النووي بصورة عامة بالإضافة الى جينات محددة بصورة خاصة، ووكون علامة المثيل الطبيعية تسهم في تنظيم التعبير الجيني، فأن هذا الاضطراب الجزيئي يساهم في اختلال الوظائف الخلوية الطبيعية ونشوء مرض ابيضاض الدم النخاعي الحاد . و تدعم نتائج مقالة المراجعة هذه التأثير المهم لطفرات جين نازعة هيدروجين إيزوسيترات على الجينات المرتبطة بمثيلة الحمض النووي في ابيضاض الدم النخاعي الحاد . و يوفر فهم التفاعل بين طفرات الجين وخلل تنظيم مثيلة الحمض النووي نظرة استكشافية لمسببات مرض ابيضاض الدم النخاعي الحاد والتنبؤ بتطوره ومجالات واعدا لتطوير العلاجات الاستهدافية.

الكلمات المفتاحية: AML، نازعة هيدروجين الأيزوسيترات ، IDH، مثيلة الحمض النووي DNA methylation ، DNA methyltransferases، بروتينات TET ، العلاج الموجه.