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Comprehensive in-Silico Characterization of Deleterious *IDH2* Variants and Their Structural and Functional Implications in Acute Myeloid Leukemia

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ABSTRACT

Mutations in the *isocitrate dehydrogenase* 2 (*IDH2*) gene are frequently implicated in the pathogenesis of acute myeloid leukemia (AML). **Objectives:** To comprehensively evaluate the structural and functional consequences of deleterious single nucleotide polymorphisms (SNPs) in the *IDH2* gene using an integrative in silico approach. **Methods:** SNP data were retrieved from public databases, and multiple bioinformatics tools were employed to predict pathogenic variants, Structural stability, conformational changes, Conservation analysis, RNA folding alterations, and protein-protein interactions. **Results:** A total of 10 high-confidence deleterious SNPs were identified, predominantly located in evolutionarily conserved regions. These variants significantly affected protein stability, increased hydrophobicity, disrupted structural conformation, and reduced protein-protein interaction affinity. RNA folding analysis further suggested altered transcript stability. **Conclusions:** Collectively, these findings highlight the potential of *IDH2* variants as molecular markers in AML and provide insights into their structural and functional implications. This study underscores the importance of integrative computational approaches in prioritizing clinically relevant mutations and may facilitate future experimental and therapeutic investigations.

INTRODUCTION

Acute myeloid leukemia (AML) is a clinically heterogeneous hematological malignancy with an annual incidence of 3–5 per 100,000 and a 5-year survival rate below 30% in adults. Despite therapeutic advances, high relapse rates and genetic diversity continue to drive poor outcomes. These challenges have prompted a deeper investigation into the recurrent genetic alterations that underlie leukemogenesis, including mutations in the *IDH2* gene [2]. AML is a very complex disease in which mutations in the genes *FLT3*, *NPM1*, *DNMT3A*, *TET2*, and *IDH1/IDH2* are recurrent and play a role in leukemogenesis by disrupting normal hematopoietic differentiation and epigenetic regulation [3]. *IDH2* mutations are found in 8–19% of AML cases, particularly in cytogenetically normal disease, and are associated with distinct clinical features including increased blast counts and specific outcomes. These mutations confer a neomorphic activity that produces 2-hydroxyglutarate, leading to epigenetic dysregulation and blocked myeloid differentiation. Importantly, *IDH2* status has therapeutic implications, as mutant-selective inhibitors such as enasidenib are now part of the AML treatment armamentarium. [4]. Under normal

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circumstances, the *IDH2* enzyme catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG), which is essential for cellular metabolism and redox homeostasis, producing NADPH. Mutations at hotspot residues, however, give rise to a neomorphic enzymatic activity, which converts α-KG to the oncometabolite 2-hydroxyglutarate (2-HG). 2-HG disrupts α-KG-dependent dioxygenases, resulting in DNA and histone methylation, altered cell differentiation, and increased proliferation of hematopoietic progenitor cells [5, 6]. Because mutant *IDH2* drives leukemogenesis through the oncometabolite 2-HG and is targetable by specific inhibitors, it represents both a prognostic biomarker and a therapeutic opportunity in AML. This dual relevance underscores the need to understand how different *IDH2* variants affect protein structure and function. [8]. Given the existence of high-resolution *IDH2* crystal structures and the large number of uncharacterised missense variants, computational mutagenesis provides a rapid and cost-effective first filter to prioritise mutations for experimental follow-up. In silico predictions can efficiently assess structural stability, interaction networks, and evolutionary conservation, offering mechanistic hypotheses that guide targeted functional assay. Facilitating the development of novel therapeutic elements, along with drug response, for this lethal disease [9].

The mutations in *IDH2* have been studied in AML; however, most studies have been centered on particular hotspot mutations or a single computational method. Previous studies on *IDH2* mutations have largely focused on individual hotspot variants or employed single computational tools, leaving the full spectrum of deleterious variants uncharacterised. Furthermore, the combined structural, stability, and interaction effects of non-canonical mutations have not been systematically evaluated. This fragmented knowledge limits our ability to predict which variants are functionally relevant and clinically actionable. This study has three specific aims: (1) to identify high-confidence deleterious missense SNPs in *IDH2* using a consensus of pathogenicity prediction tools; (2) to assess the impact of these variants on protein stability, conformation, and RNA folding; and (3) to evaluate how these mutations alter protein-protein interaction affinities. We hypothesise that deleterious variants cluster in conserved functional domains and consistently destabilise the IDH2 structure.

METHODS

This is an in-silico study which was carried out at the Department of Zoology, Division of Science and Technology, University of Education Lahore, Lahore, Pakistan from January 2025 to June 2025. The data were retrieved after obtaining approval from the Department of Zoology, Division of Science and Technology, University of Education Lahore, Lahore, Pakistan. All the missense SNPs of the IDH2 gene were obtained from the database of single nucleotide polymorphisms (dbSNP). PolyPhen-2, PROVEAN, PhD-SNP, Align-GVGD, and SNAP2 were used to screen variants. Variants were retained only if they met consensus cutoffs: PolyPhen-2 ≥ 0.85 ("probably damaging"), PROVEAN ≤ −2.5 ("deleterious"), PhD-SNP > 0.5 ("disease"), Align-GVGD = C65, and SNAP2 score > 50 ("strong effect"). This strict multi-tool consensus yielded the final ten missense SNPs for downstream analyses. After filtering, the resulting ten variants were candidates. Protein interaction information was retrieved from STRING, evolutionary conservation was assessed by ConSurf, and SWISS-MODEL was used to build protein structural models. The data were retrieved from all databases from January to June 2025. The gene information for human IDH2 was downloaded from the NCBI Gene database (Gene ID: 3418), and the protein sequence was retrieved from the UniProtKB database (Accession No.: P48735; Entry: IDHP_HUMAN). This study uses the reference transcript and protein sequences corresponding to NM_002168.4 and NP_002159.2, respectively, of the NCBI RefSeq database. The variants of the gene IDH2 were considered as missense variants by checking with the dbSNP database. Using STRING (Protein ID: 9606), a protein-protein interaction analysis was performed. ENSP00000331897). The SWISS-MODEL server generated 3-D models of the structure based on the structure of the UniProt sequence (Accession No. P48735), and the server selected the templates automatically based on sequence homology. The use of several prediction tools was to ensure that the prediction was not biased and the result was reliable because of consensus evaluation. To anticipate the influence of amino acid alterations on protein stability, I-Mutant Suite and mCSM were used. ConSurf was used to calculate the conservation profile of amino acid residues in the protein sequence in the form of a grade. NetSurfP was used to analyze the surface accessibility factor, secondary structure, disorder, and phi/psi dihedral angles of amino acids in the protein sequence. HOPE was used to anticipate the influence of amino acid changes on protein structure and function.

The mutant and wild-type protein models were constructed by evaluating the similarity score and recovery value from a table of templates using SWISS-MODEL. MolProbity was used to test the validity of protein models, and ProtParam was used to examine their physical and chemical characteristics. UCSF Chimera 1.5.3 was utilized to superimpose the structures of wild type and mutant type. Any structural change and the extent of similarity or difference between two structures were inspected by overlapping both wild-type and mutant models. PyMOL was used to visualize a 3D representation of the protein

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sequence as well as to locate the site of mutant residues. The influence of all *IDH2* SNPs on RNA folding was evaluated through the Vienna package. STRING database was used to find the association of the *IDH2* protein with related proteins. To observe the impact of SNPs on protein-protein interactions, mCSM-PP12 was operated. workflow chart has been given (Figure 1).

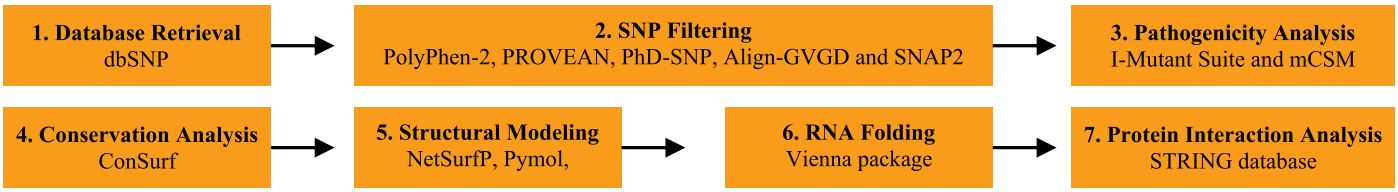

Figure 1: Work Flowchart

RESULTS

IDH2 gene has 3 isoforms. 5 SNPs (R140L, R140W, R172W, R172G, and R172M) were found on isoform 1, while the other 5 SNPs (R88L, R88W, R120W, R120G, and R120M) were found on isoform 2. All amino acid substitutions were found to be detrimental, deleterious, and disease-causing (Table 1).

Table 1: Analysis of SNPs in the *IDH2* Gene and the Subsequent Effect of Amino Acid Changes on Protein Structure by Using Various in Silico Programs

DBSNP RS#	SNPs	Polyphen-2 (0.000-1.000)	PROVEAN (Typically, 0 to Negative Values)	PhD-SNP (0 – 1)	Align GVGD (C0 – C65)	SNAP2 (score/ Accuracy) (-100 – +100)
rs121913502	R140L	Damaging	Deleterious	Disease	C65	Effect
rs121913502	R88L	Damaging	Deleterious	Disease	C65	Effect
rs1057519906	R120W	Damaging	Deleterious	Disease	C65	Effect
rs1057519906	R120G	Damaging	Deleterious	Disease	C65	Effect
rs267606870	R140W	Damaging	Deleterious	Disease	C65	Effect
rs1057519906	R172W	Damaging	Deleterious	Disease	C65	Effect
rs267606870	R88W	Damaging	Deleterious	Disease	C65	Effect
rs1057519906	R172G	Damaging	Deleterious	Disease	C65	Effect
rs121913503	R120M	Damaging	Deleterious	Disease	C65	Effect
rs121913503	R172M	Damaging	Deleterious	Disease	C65	Effect

Polyphen-2: Closer to 1 (Damaging), PROVEAN: ≤ -2.5 (Deleterious), PhD-SNP: C45–C65 (Deleterious), SNAP2 (score/Accuracy): > +50 (Strong effect), dbSNP: database of single nucleotide polymorphism, snp: single nucleotide polymorphism, r: arginine, w: tryptophan, m: methionine, g: glycine, l: leucine

I-mutant Suite analysis showed that 8 out of 10 mutated variants (R140W, R172G, R120M, R172M, R172W, R120W, R120G, R88W) decrease the structural stability, while the remaining 2 (R140L and R88L) increase the protein stability. Furthermore, mCSM discovered all SNPs destabilizing the protein structure (Table 2).

Table 2: Predicted Effect of *IDH2* SNPs on Protein Stability

DBSNP RS#	SNP	I-Mutatnt3.0		mCSM	
		DDG Value (Kcal/mol)	Stability	ΔΔG (kcal/mol)	Stability
rs121913502	R140L	0.04	Increase	-0.764	Destabilizing
rs267606870	R140W	-0.17	Decrease	-1.151	Destabilizing
rs1057519906	R172G	-0.93	Decrease	-1.624	Destabilizing
rs121913503	R120M	-0.18	Decrease	-0.946	Destabilizing
rs121913503	R172M	-0.18	Decrease	-0.871	Destabilizing
rs121913502	R88L	0.04	Increase	-0.876	Destabilizing
rs1057519906	R172W	-0.39	Decrease	-1.096	Destabilizing
rs1057519906	R120W	-0.39	Decrease	-1.248	Destabilizing
rs1057519906	R120G	-1.58	Decrease	-1.62	Destabilizing
rs267606870	R88W	-0.17	Decrease	-1.226	Destabilizing

DDG: Change in Gibbs free energy, ΔΔG: Difference in Protein Stability after mutation, Kcal/mol: kilocalorie per mole

ConSurf predicted that all these SNPs were observed within a highly conserved area (conservation value = 9). NetSurf P 2.0 showed 70% of mutant residues as buried and 30% as exposed (Table 3).

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Table 3: Analysis of the Evolutionary Conservation Profile of SNPs in the *IDH2* Gene by ConSurf

DBSNP RS#	SNPs	ConSurf		
		Conservation Score	Exposed	Functional
rs121913502	R140L	9	Exposed	Functional residue
rs267606870	R140W	9	Exposed	Functional residue
rs1057519906	R172G	9	Exposed	Functional residue
rs121913503	R120M	9	Exposed	Functional residue
rs121913503	R172M	9	Exposed	Functional residue
rs121913502	R88L	9	Exposed	Functional residue
rs1057519906	R172W	9	Exposed	Functional residue
rs1057519906	R120W	9	Exposed	Functional residue
rs1057519906	R120G	9	Exposed	Functional residue
rs267606870	R88W	9	Exposed	Functional residue

As interpreted by HOPE, 6 mutant residues (R140L, R172G, R120M, R172M, R88L, and R120G) were smaller than wild type, while R140W, R172M, R120W, and R88W were bigger. Hydrophobicity was shown to increase in all mutant amino acids (Figure 2).

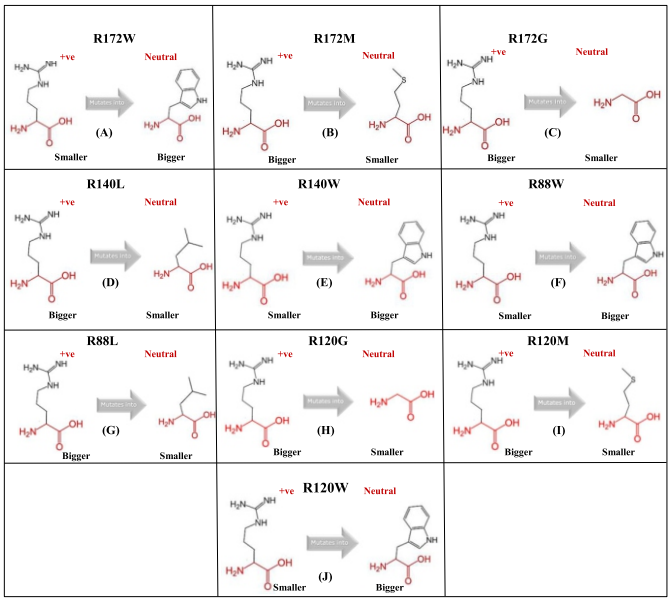

Figure 2: Native (left) and Mutant (Right) Amino Acid Residues of *IDH2* Gene Mutations (A) R172W, (B) R171M, (C) R172G, (D) R140L, (E) R140W, (F) 8W, (G) R88L, (H) R10G, (I) R120M, (J) R120W

SWISS-MODEL indicated that the models built for wild type and mutant type are correct. Protpram analyzed that there was a difference in the physicochemical parameters of proteins of the target gene between the mutant and wild type among all variants of isoforms 1 and 2 (Table 4).

Table 4: Contrasting Physicochemical Parameters of Normal and Mutated Proteins of the Targeted Gene

Isoform 1						
Parameters	Wild	Mutants				
		R140L	R140W	R172W	R172G	R172M
Number of Amino Acids	452	452	452	452	452	452
Molecular Weight	50909.28	50866.25	50866.25	50866.25	50866.25	50866.25
Theoretical PI	8.88	8.80	8.80	8.80	8.80	8.80
Instability Index	29.77	29.92	29.77	30.14	29.62	30.61
Aliphatic Index	77.26	78.12	77.26	77.26	77.26	77.26
GRAVY	-0.397	-0.379	-0.389	-0.389	-0.388	-0.383
Isoform 2						
Parameters	Wild	Mutants				
		R88L	R88W	R120W	R120G	R120M
Number of Amino Acids	398	398	398	398	398	398
Molecular Weight	44961.35	44918.32	44991.38	44991.38	44862.22	44936.36
Theoretical PI	7.63	7.18	7.18	7.18	7.18	7.18
Instability Index	23.10	23.27	23.10	23.52	22.92	24.05
Aliphatic Index	77.66	78.64	77.66	77.66	77.66	77.66
GRAVY	-0.404	-0.383	-0.395	-0.395	-0.394	-0.388

GRAVY: grand average of Hydropathicity, PI: Theoretical Isoelectric point

For *IDH2* isoform 1, the data obtained from Ramachandran plots of MOLPROBITY showed that the favoured region contained 96.1%-96.8% of the residues, whereas the allowed region contained 100.0 percent of the residues. For *IDH2* isoform 2, it showed 95.6%- 96.6% residues in favored regions and 99.6%-100.0% residues falling in the allowed region. With respect to the native protein structure, the location of mutant amino acid residues was validated in these regions (Figure 3).

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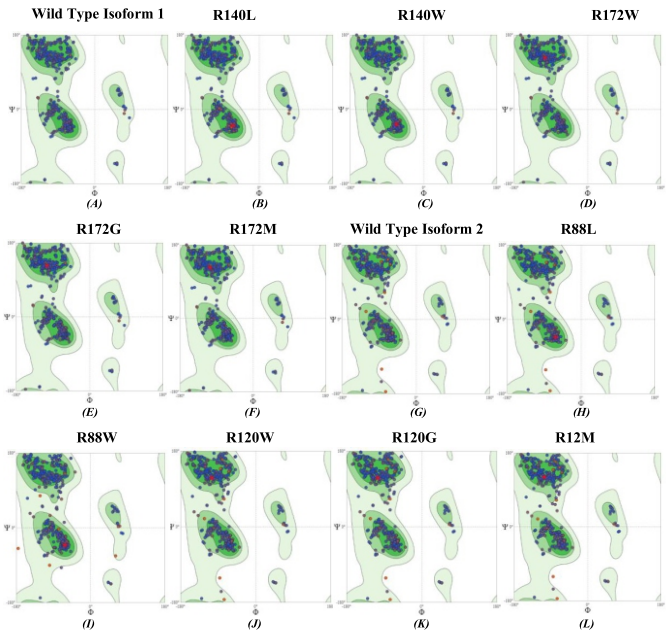

Figure 3: Percentage of Amino Acid (A) Wild type isoform 1, (B) mutation R140L, (C) R140W, (D) R172W, (E) R172G, (F) R172M, (G) Wild type isoform 2, (H) R88L, (I) R88W, (J) R120W, (K) R120G, (L) R120M of *IDH2* gene in Acute Myeloid Leukemia Patients in Allowed and Favored Region of Ramachandran Plot Taken Through Swiss Model

UCSF Chimera showed the superimposed structures of wild-type and mutant *IDH2* models representing the SNPs in the highlighted area (Figure 4).

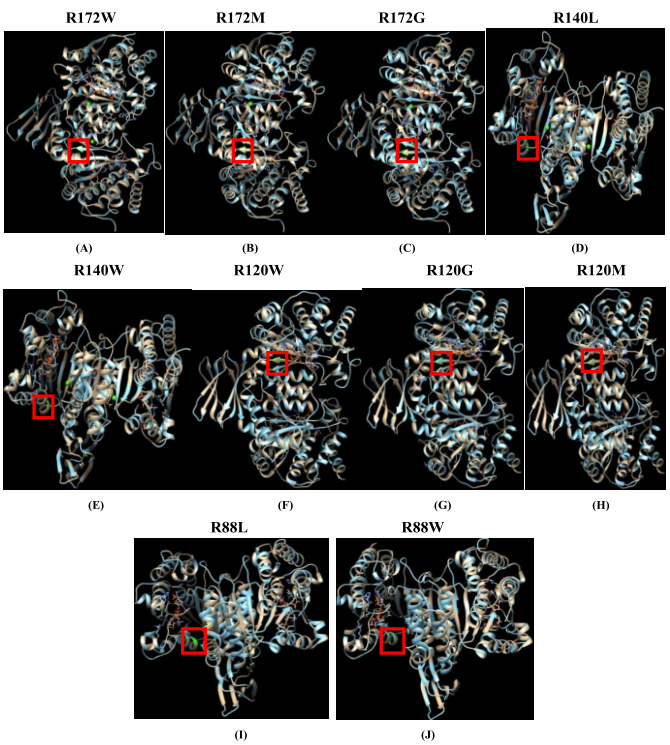

Figure 4: The Amino Acid Substitution of (A) R172W, (B) R172M, (C) R172G, (D) R140L, (E) R140W of IDH2 Gene Isoform 1, and (F) R120W, (G) R120G, (H) R120M, (I) R88L, (J) R88W of *IDH2* Gene Isoform 2, in the Superimposed Model of Mutants Over Wild Type Structures, Using UCSF Chimera

PyMOL with Project HOPE presented the wild-type and mutant residues on the protein structure of the *IDH2* gene of Acute Myeloid Leukemia Patients. This illustration was done by PYMOL and Project HOPE (Figure 5).

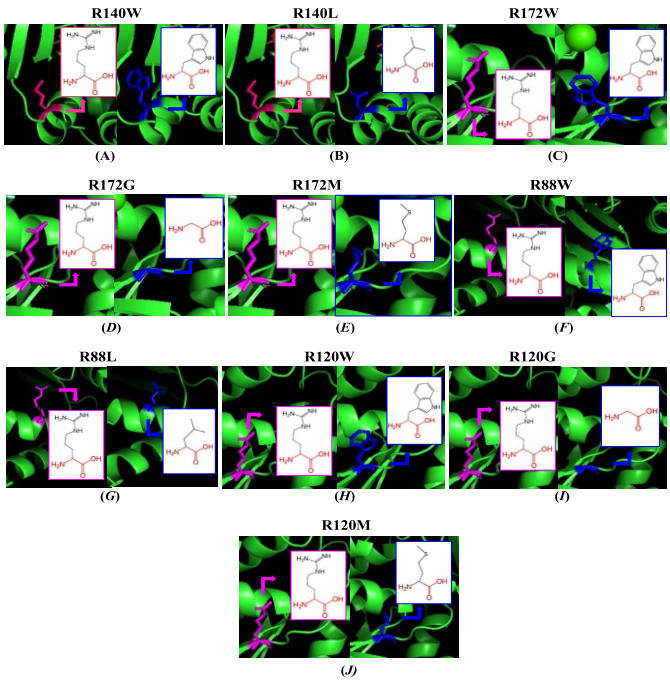

Figure 5: (A) R140W, (B) R140L, (C) R172W, (D) R172G, (E) R172M, (F) R88W, (G) R88L, (H) R120W, (I) R120G, (J) R120M Showing Amino Acid Arginine Changes to Tryptophan at Position 140,172, and 88 to Leucine at position 140 and 88, to Glycine at Position 172 and 120, and to Methionine at Position 172 and 120

DISCUSSION

The *IDH2* gene was selected because recurrent *IDH2* SNPs are frequently reported in AML. There have been a few computational studies covering *IDH2* mutations, but mostly only mutations or individual computational methods. In the present study, pathogenicity prediction, conservation analysis, structural modeling, RNA folding analysis, and assessment of protein interaction are combined within a single approach. Disease-causing SNPs are most commonly discovered in evolutionarily conserved locations [10]. The SNPs determined in this study can be utilized in the prognosis of AML. The focus was on the coding area, which revealed 10 SNPs in the *IDH2* gene using an exclusive series of bioinformatics approaches. All of the Non-synonymous coding SNPs (R140W, R172G, R120M, R172M, R172W, R120W, R120G, R88W, R88M, R140L) were found highly pathogenic. In a previous study, it was stated that enzymatic active sites are affected by pathogenic *IDH2* SNPs; these are the sites where isocitrate and cofactor NADPH bind [11]. Highly pathogenic mutations in the *IDH2* gene can increase the prevalence in intermediate-risk AML

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patients [12]. The assessment of several SNPs on the protein structure revealed that they can disrupt interactions with other neighboring molecules. I-mutant Suite and mCSM projected that the SNPs would reduce the stability of the *IDH2* protein, which determines the structure and appropriate functioning of proteins. By using ConSurf and NetSurf, it was observed that the residues predicted to be mutated in all SNPs were evolutionarily conserved, indicating the SNPs to be highly deleterious [13]. Project HOPE server revealed discrepancies in size and charge of the mutant amino acid as compared with the wild type. The mutant residues were either smaller or larger than the wild type; they lost their positive charge and became neutral, which can cause them to lose their interactions with the nearby molecules. Also, the mutant residues were more hydrophobic than the wild type, disrupting the correct folding. All these differences can create a disorder, disturb the H-bonding with the nearby amino acids, and destroy the protein framework. As presented in a study, the SNPs in highly conserved regions can modify the cell cycle regulation [14]; SNPs can disrupt amino acid associations directly or indirectly, causing structural and functional abnormalities in the *IDH2* protein at a certain point. Various cellular and metabolic mechanisms can be disrupted, such as energy (ATP) production and NADPH synthesis by the neomorphic enzymatic activity of the mutant *IDH2* protein , which is necessary for fatty acid and lipid synthesis, increasing the percentage of myeloid blasts and worsening the condition of AML patients [15]. Vienna Package predicted an aberrant RNA folding of mutant residues from the wild type. Abnormal RNA folding can affect the localization of mRNA and protein translation, resulting in altered function in the mutant *IDH2* protein, causing increased myeloid blast percentage in AML-affected persons [16]. The findings of Swiss-Model, ProtParam, Molprobity, UCSF, Chimera, and PyMOL revealed that the altered residues were positioned in a region critical for the protein's activity, and that other residues were in connection with it, suggesting that these interactions were important for the protein's proper functioning. The SNPs can alter these interactions and may disturb the *IDH2* protein and abolish its correct functioning by introducing amino acids with different properties. The analysis of mCSM indicated that all mutations cause a decrease in protein-protein interaction, resulting in protein destabilization. The discrepancy between the prediction of I-Mutant Suite and mCSM was detected for the two variants (R140L and R88L). Stability predictions: I-Mutant predicted increase; destabilizing (mCSM). All these genes produce 5 unique enzymes, which contribute to achieving a similar function, that is, the citric acid cycle. The ACO2 enzyme is responsible for the conversion of citrate to isocitrate via cis-aconitate. Isocitrate (ICT) is decarboxylated into alpha-ketoglutarate by *IDH3A* (Catalytic subunit), *IDH3B* (Non-Catalytic subunit), and *IDH3G* (Regulatory subunit) of the isozyme *IDH3*. OGDH is the enzyme involved in the ultimate conversion of 2-oxoglutarate to succinyl-CoA and CO (2). This cascade of events is interrupted when the mutant *IDH2* enzyme is produced, which is not able to convert isocitrate to α-ketoglutarate [17]. Rather, it develops a neomorphic enzymatic activity capable of producing 2-hydroxyglutarate from-ketoglutarate, altering the overall Krebs' cycle and leading to aberrant DNA hypermethylation, a halt in differentiation of myeloid precursors, and eventually promoting leukemogenesis. Thus, at the time of presentation, AML patients with *IDH2* mutations have a higher platelet count, a higher bone marrow and peripheral blast fraction, and a high percentage of neutrophils [18]. To enhance the translational relevance of the findings, the identified mutations correspond to previously reported hotspot residues (R140 and R172), which are clinically associated with AML prognosis and targeted therapy response, including *IDH2* inhibitors such as enasidenib [19, 20]. The structural destabilization observed in this study may contribute to altered enzymatic activity and oncometabolite production, supporting their role in leukemogenesis.

There are several limitations in this study. First, findings were all made based on computational predictions and not validated experimentally. Second, the number of variants tested (ten) may not be exhaustive of the range of mutations in *IDH2*. Thirdly, the predicted pathogenic effects were not validated using clinical datasets. Hence, future investigation using functional assays, molecular dynamics simulations, and clinical validation is needed to validate these variants for their biological relevance.

CONCLUSION

Gene variations are believed to play a crucial impact on a variety of human disorders. In this study, it was determined that R140L, R140W, R172W, R172G, R172M, R88L, R88W, R120W, R120G, and R120M are pathogenic mutations, which have a possible functional influence. These SNPs can lead to a mutant *IDH2* enzyme that is unable to perform its normal function, leading to the development of acute myeloid leukemia. Some of these variations could be considered as possible candidate biomarkers, and further experimental and clinical studies are needed to confirm the diagnostic or prognostic importance, considering the large variety of AML among different ethnicities. These findings may assist in prioritizing *IDH2* variants for future validation studies and targeted therapeutic interventions in AML patients.

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Authors' Contribution

Conceptualization: AMA
Methodology: AMA
Formal analysis: AMA
Writing and Drafting: AMA, HN, SC, HZ, ZI
Review and Editing: AMA, HN, SC, HZ, ZI

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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