# Frequency and Distribution of IDH1 and IDH2 mutations in AML Cases with a Normal Karyotype in Pakistan

**HS Pal MBBS, FCPS[1], U Saleem MBBS, MD, FCPS[2], MA Naveed MBBS, FCPS, PhD[2], A Aleem Bsc MLT[2]**

1. Aga Khan University Hospital, Lahore, Pakistan
2. University of Health Sciences, Lahore, Pakistan

## Introduction

Acute Myeloid Leukemia (AML) is a well-established entity with numerous genetically driven mutations. Various molecular alterations include mutations in isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2)[1]. These mutations produce 2-hydroxyglutarate (2-HG), a metabolite that interferes with normal hematopoietic differentiation leading to development of leukemia[2]. Identifying the frequency and distribution of these mutations is essential for risk stratification and targeted therapeutic interventions[3], particularly in populations with limited genetic data on AML[4].

## Aim

This study aimed to determine the frequency and distribution of IDH1 and IDH2 mutations in primary AML cases with a normal karyotype in Pakistan.

## Methods

**Study Design**: Cross sectional Descriptive study

**Duration**: 2023-2024

**Settings:** This prospective study was conducted at Aga Khan University Hospital, Regional Lab, Lahore and University of Health Sciences, Lahore, Pakistan.

**Materials & Methods:** Total 135 newly diagnosed primary AML adult patients with a normal karyotype were enrolled. Genetic screening for IDH1 (R132H) and IDH2 (R140Q, R172K) mutations was performed utilizing allele-specific polymerase chain reaction (PCR). To ensure accurate differentiation between wild-type and mutant alleles, primers (mutation-specific) were designed to detect single nucleotide variations with high specificity.

## Results

Among the 135 AML patients 79 (58.5%) were males while 56 (41.5%) were females with median of 39 years (range 18-65) as described in Figure1.

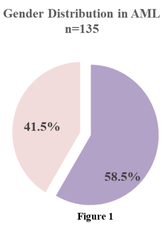



**Figure 1**

IDH1 mutations were detected in 12% (16/135), and IDH2 mutations were identified in 11% (15/135) shown in Figure 2.

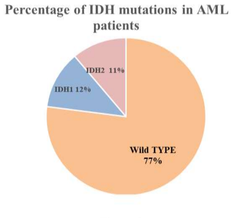



**Figure 2**

Various alleles are shown in Figure 3 identified in this study.

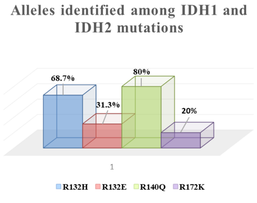



**Figure 3**

Distribution of various IDH mutations that was found in AML patient is being projected in Figure 4.

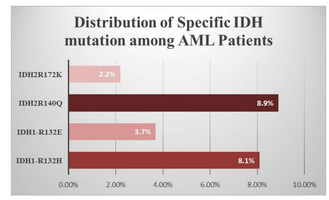



**Figure 4**

Comparison of findings with other studies is mentioned in Table 1:

Table:1

| Authors/ location | Duration | No. of Patients | Age (years) Median & Range | Gender Distribution M:F | Frequency of IDH1/IDH2 mutations | Frequency of specific alleles | Cytogenetics |
|---|---|---|---|---|---|---|---|
| Current Study Pal HS et al Lahore-Pakistan | 2023-24 | 135 | 39 (18–65) | 1.4:1 | IDH1: 12% IDH2: 11% | R132H: 8.1% R132C: 3.7% R140: 8.9% R172: 2.2% | Normal Karyotype in 100% IDH$^{mut}$ |
| Abbas SH et al Karachi-Pakistan | 2023-24 | 73 | 48 (15-70) | 1.5:1 | IDH1: 4% IDH2: NA* | R132: 4% R140: NA* R170: NA* | Normal Karyotype in 100% IDH$^{mut}$ |
| Kapoor P et al Lucknow-India | 2019-23 | 100 | 37 (18-56) | 1:1.6 | IDH1: 19% IDH2: 06% | NA* | Normal Karyotype in 8% with IDH$^{mut}$. Remaining were not tested. |
| Messina M et al Bologna-Italy | 2017-20 | 284 | 65 (19-86) | 1.4:1 | IDH1: 14% IDH2: 18% | R132: 11% R140: 10% | Normal Karyotype |
| Courtney D. et al Texas-USA | 2010-14 | 826 | 62 (18–92) | 1.7:1 | IDH1:7.1% IDH2:12.8% | R132: 7% R140: 10% R170: 3% | Normal karyotype and intermediate risk +8, del(9q), del(20q), t(9;11). in 77% of IDH$^{mut}$ |
| Schnittger S et al. Munich-Germany | 2005-09 | 1414 | 66 (17-93) | 1.8:1 | IDH1:6.6% IDH2: NA* | R132: 6.6% | 10% of normal karyotype had IDH$^{mut}$ |

*NA: Not Available

The IDH1-R132H and IDH2-R140Q mutations were the most prevalent, consistent with international data. IDH mutations have been significantly associated with normal karyotype AML, suggesting a potential role in leukemia pathogenesis and prognosis.

## Conclusion

This study highlights the frequency and distribution of IDH1 (12%) and IDH2 (11%) mutations in normal karyotype primary AML cases in Pakistan, with IDH1-R132H and IDH2-R140Q being the commonest ones. These findings highlight the importance of conducting routine molecular screening using allele-specific PCR for early identification of IDH mutations in AML. Future studies with larger cohorts and longitudinal follow-ups are required to explore the full clinical implications of IDH mutations in AML.

## References

1.Zarnegar-Lumley S, Alonzo TA, Gerbing RB, Othus M, Sun Z, Ries RE, Wang J, Leonti A, Kutny MA, Ostronoff F, Radich JP. Characteristics and prognostic impact of IDH mutations in AML: a COG, SWOG, and ECOG analysis. Blood Advances. 2023 Oct 10;7(19):5941-53.

2.Montalban-Bravo G, DiNardo CD. The role of IDH mutations in acute myeloid leukemia. Future Oncol. 2018 Apr;14(10):979-993. doi: 10.2217/fon-2017-0523. Epub 2018 Mar 15. PMID: 29543066.

3.Issa GC, DiNardo CD. Acute myeloid leukemia with IDH1 and IDH2 mutations: 2021 treatment algorithm. Blood cancer journal. 2021 Jun 3;11(6):107.

4.Shahid S, Shakeel M, Siddiqui S, Ahmed S, Sohail M, Khan IA, Abid A, Shamsi T. Novel genetic variations in acute myeloid leukemia in Pakistani population. Frontiers in Genetics. 2020 Jun 23;11:560.