GENOMIC LANDSCAPE OF COPY-NEUTRAL LOH AND CNA IN INTERMEDIATE-RISK AML: RECURRENT ALTERATIONS IN PHF6, SMC1A, AND KMT2A GENES

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Introduction

The copy number alteration (CNA) and copy-neutral loss of heterozygosity (cnLOH) significantly contribute to the mutational profile of AML. In this study, we examined CNA and cnLOH in genes whose mutations are known to play a crucial role in the pathogenesis of AML.

Aim

To identify CNA and cnLOH in *NPM1, CBL, FLT3, JAK2, KIT, KRAS, MPL NRAS,CALR,CSF3R, DNMT3A, IDH1, IDH2 TET2, ASXL1, BCOR, BCORL1, EZH2, KMT2A SETBP1, NF1, PHF6, TP53, WT1, CEBPA, ETV6 GATA2, RUNX1, SF3B1, SRSF2, U2AF1, ZRSR2 RAD21, SMC1A, SMC3,* and *STAG2* gene in tumor genomes of intermediate risk AML patients using CMA.

Methods

We included 34 patients with AML who were treated at the National Medical Research Center for Hematology between 2017 and 2022. All patients belonged to intermediate risk group according to ELN-2022. Most of the patients (29/34) had normal karyotype. Two patients had karyotype not belonging to good or adverse group and in 4 cases karyotype could not be determined due to the absence of mitosis, although FISH ruled out adverse aberrations. FLT3-ITD mutations were found in 13/34 (38%) of patients. CMA was performed on tumor DNA obtained during the primary diagnosis either from fresh samples or from archival material. CMA was carried out with Thermo Fisher Scientific equipment using the CytoScan™ HT-CMA 96F array SNP-oligonucleotide microarray in accordance with the manufacturer's protocol. Data were analyzed using Chromosome Analysis Suite and processed with Python 3.12.4 and SAS 9.4. We compared our CMA data with a triple-matched control dataset from 102 ostensibly healthy individuals (HI).

Summary

The high frequency of cnLOH (virtually, the homozygotizing of mutations) in the *PHF6*, *SMC1A*, and *BCOR* genes may suggest their role as "second hits" in leukemia development. On the other hand, KMT2A alterations represent specific drivers of the disease (Fig.3).

Results

- The most frequent events were cnLOH of PHF6 (55.88% in patients vs 44.12% in HI), *SMC1A* (53.94% in patients vs 53.92% in HI), *BCORL1* (50% in patients vs 36.27% in HI) and *BCOR* (35.29%in patients vs 32.35% in HI) (Fig.1).
- In contrast gain of *KMT2A* (14.71%) and cnLOH *KMT2A* (8.82%) were revealed only in patients (Fig.1,2).

Figure 1. Frequency of copy number aberrations and cnLOH of genes associated with leukemogenesis in patients with intermediate prognosis AML (n=34) and in subjects from the comparison group (n=102).

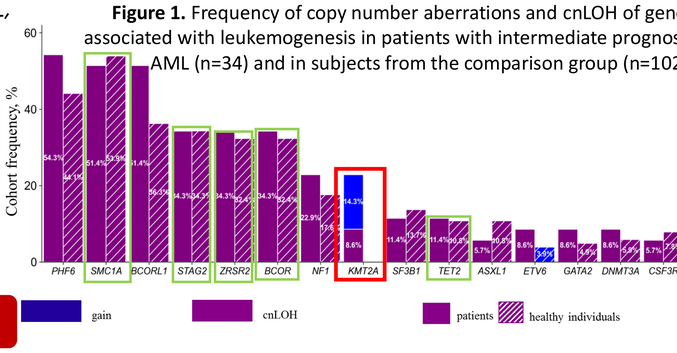


Figure 2. Localization of different types of aberrations in the *KMT2A* gene region

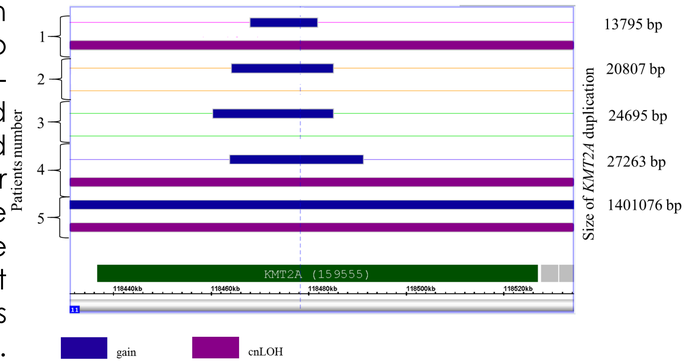
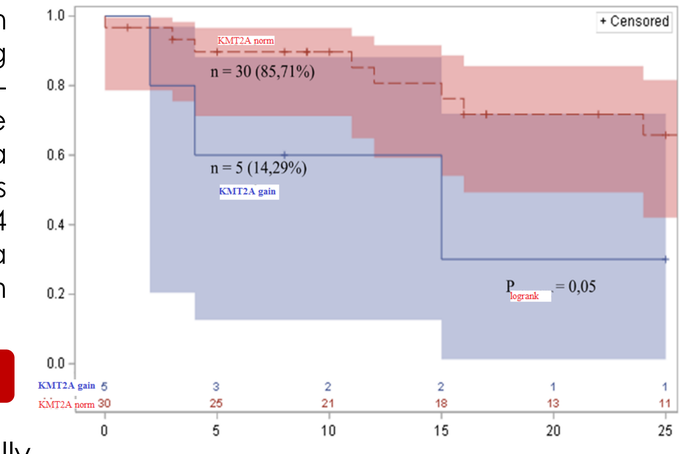


Figure 3. KMT2A gene duplications are associated with a worse overall survival (Plog-rank=0.05)



Acknowledgment

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