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Acute Leukemias

GENOMIC SCREENING OF PRIMARY REFRACTORY ACUTE MYELOID LEUKEMIA WITHOUT TP53 ALTERATIONS BY OPTICAL GENOME MAPPING (OGM)

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Introduction: Approximately 10-30% of adults with acute myeloid leukemia (AML) experience persistent leukemia following intensive induction therapy. To date, management of these patients remains challenging due to low response rate to savage chemotherapy and poor overall survival (OS) rate.
Methods: Diagnostic samples from bone marrow (BM) were analyzed by conventional cytogenetics and next-generation sequencing (NGS). Optical genome mapping (OGM) is a new genome-wide technology that can detect structural genomic variations (SVs), copy number variations and whole-chromosome aneuploidies with high resolution. In the present study, available cryopreserved mononuclear cells were processed to obtain Ultra-high molecular weight (UHMW) DNA samples useful to perform OGM analyses by Bionano Saphyr instrumentation.
Results: We collected a retrospective cohort of 25 patients with AML who do not achieve remission after one to two cycles of induction therapy (primary refractory AML, PR-AML). Median age at diagnosis was 60 years (range, 25-82). The median OS was 14 months. Conventional karyotyping, FISH analyses, and NGS classified 14 patients into ICC categories, including 7 AML with myelodysplasia-related cytogenetic abnormalities, 5 AML with myelodysplasia-related mutations, 1 AML with MECOM rearrangement, 1 with NPM1 mutation. NGS analyses identified mutations comprising DTA (DNMT3A, ASXL1, TET2; 50% of cases), RUNX1 (38%), IDH1 and IDH2 (38%), splicing factors (25%), RAS pathway (25%), FLT3 (19%), CSF3R (19%), WT1 (6%) and NPM1 (6%). Twelve patients (60%) showed normal karyotype, and 1 patient showed the uncommon translocation t(3;6)(q26;q24) including MECOM gene. All patients were negative for TP53 alterations (mutations and/or deletions). OGM confirmed genomic abnormalities (trisomy 8, del5q, del7q and monosomy 7 with loss of EZH2 gene, and del20q comprising TOP1 gene) identified by karyotyping and FISH, but also found additional alterations including the classifying lesion t(5;11)(q35.3;p15.4) NDS1-NUP98 translocation in two cases (Figure 1), dup(11)(q23.3; q23.3) KMT2A duplication in one case, and SVs involving MECOM gene (2 insertions and 1 allelic imbalance) in 2 cases. One patient diagnosed as AML with NPM1 mutation and normal karyotype showed two insertions in inositol triphosphate 3 kinase (ITPKB) and leukemia inhibitor factor receptor (LIFR) genes, which are RUNX1-regulated tumor-suppressors involved in HSC homeostasis and myeloid differentiation. A 14q11.2 deletion was detected in one patient with AML with normal karyotype and any mutation identified by NGS.
Conclusions: To our knowledge, the present study represents the first application of OGM technology to a selected cohort of patients with primary refractory AML, not harbouring TP53 alterations. Our data indicate that OGM can be used to identify additional structural variations relevant to improve AML classification and better define the pathogenetic alterations in this subset.

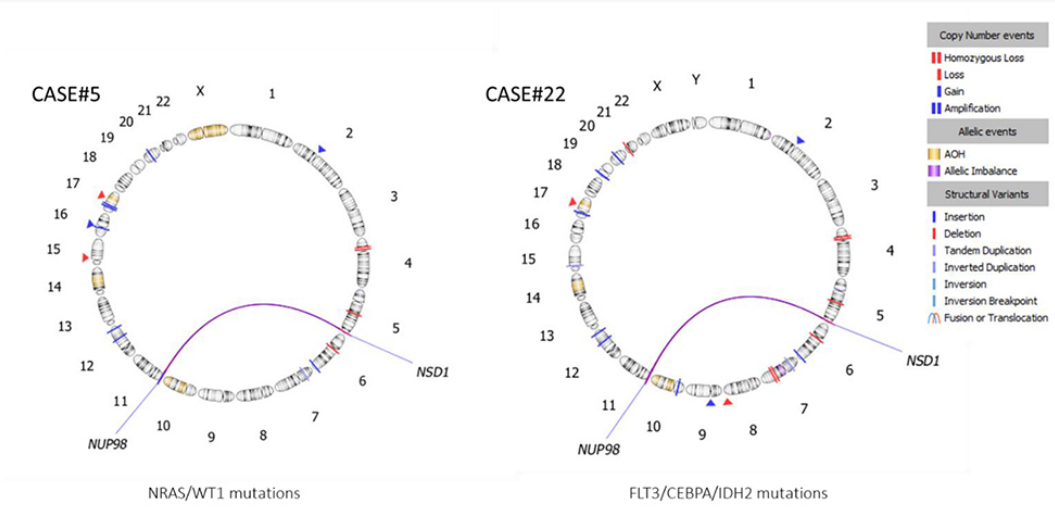

Figure 1. OGM detects t(5;11) (q35.3; p15.4) NDS1-NUP98 translocation in 2 patients with refractory AML. Circos plots showing structural variations as indicated in the legend. Mutated genes identified by NGS analyses are reported.