Exploration of the variant composition in the genome of pediatric and adult recurrent Acute Myeloid Leukemia

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BACKGROUND

Acute myeloid leukemia (AML) arises from malignant transformation of myeloid progenitor cells, overgrowing functional blood cells in the bone marrow (BM) before infiltrating peripheral blood and possibly other organs. Although most patients achieve complete remission after intensive treatment, relapse remains the leading cause of death for AML patients. Numerous studies have helped to elucidate the mutational landscape at AML diagnosis, leading to improved risk-stratification and new therapeutic options. However, multi-whole genome studies of AML relapse and primary resistant (R/PR) AML samples are necessary for further andvances.

COHORT

We studied primary sequential specimens from 48 adult and 25 pediatric AML (non-APL) patients from the Nordic countries, all of which relapsed or had primary resistant disease. The cohort comprised of diagnosis- (D, n=52), relapse- (n=80) and PR specimens (n=6), as well as normal control samples for 61 of these patients.

METHODOLOGY

DNA was obtained from purified mononuclear tumor cells and normal BM derived stromal cells using QIAGEN extraction kits. We performed whole genome or whole exome sequencing (WGS/WES) and subsequently called single nucleotide variants (SNVs), structural variants, copy number variants (CNVs) and copy-neutral loss-of-heterozygosity (CN-LOH).

RESULTS

The most frequent alteration found in adult R/PR AML was frameshift mutation in ***NPM1*** in 40.8% of cases, while none was found in children.

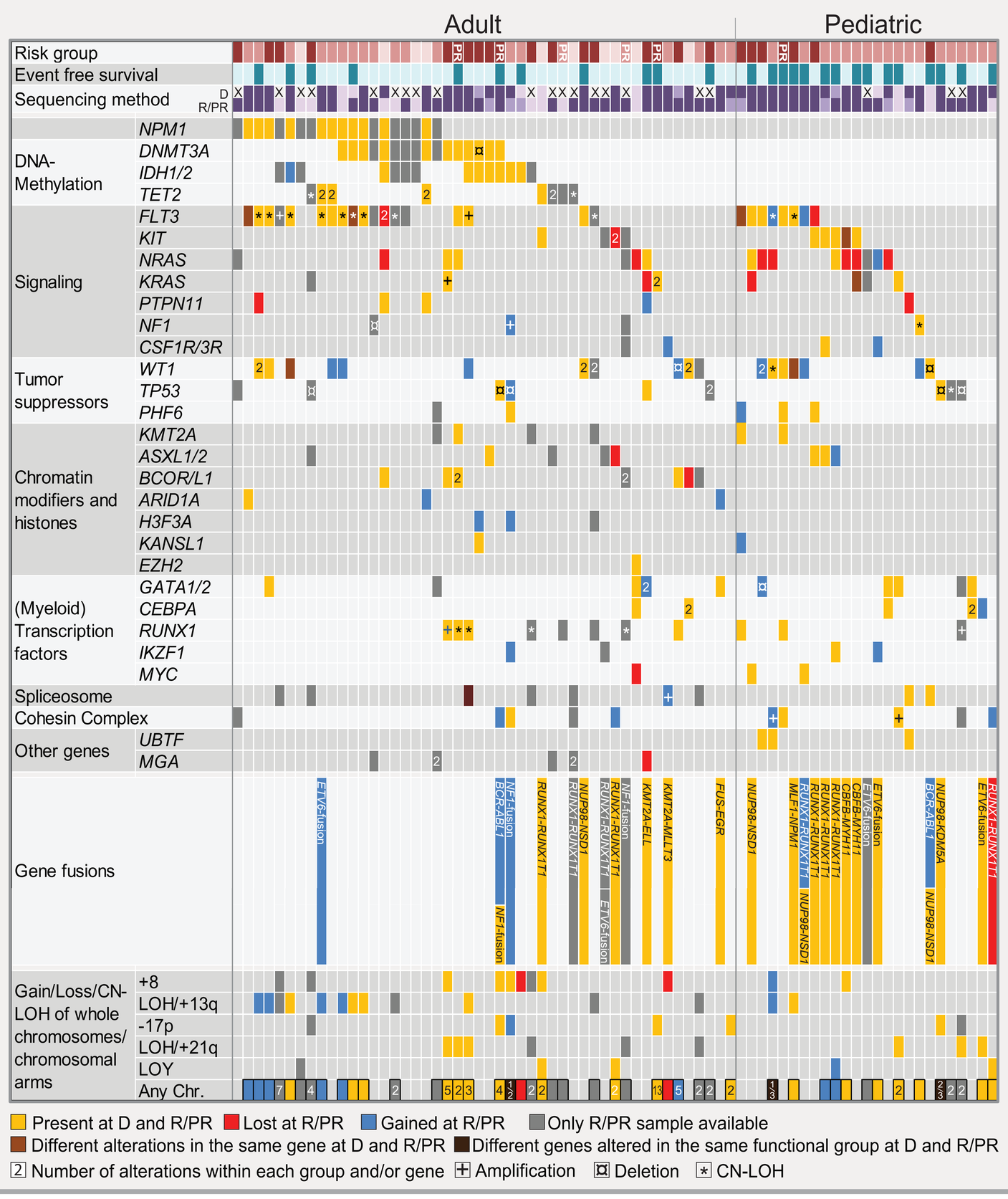
Mutations in **signaling** related genes were frequently detected as sub-clonal and unstable during disease progression.

Alterations in **tumor suppressor** genes showed increased variant allele frequency during leukemic progression.

Alterations in genes involved in **epigenetic** regulation were mostly stable or gained during tumor evolution.

Mutations in **cohesin**-associated genes recurrently appearing in refractory AML.

Structural variants and **copy number alterations** were mostly stable or gained during leukemic progression. In addition, common AML-associated gene fusions were overrepresented in pediatric AML.



We identified ***CSF1R*** mutations appearing at relapse in two cases (2.7%). Of note is that *CSF1R* mutations have not previously been reported in *de novo* AML.

H3F3A p.K28M mutations were recurrently found at relapse in adult samples (6.3%), while these mutations have not been reported at diagnosis in *de novo* AML.

We detected ***IKZF1*** alterations in 10.2% of R/PR adult AML including SNVs, focal deletions and monosomy 7, while *IKZF1* mutations have previously rarely been found in AML.

We found recurrent heterozygous in-frame internal tandem duplications in ***UBTF*** at diagnosis and relapse in three (12.0%) pediatric cases.

Loss-of-function mutations in ***MGA*** were identified at relapse in four (10.4%) adult *KMT2A*-PTD-negative AML cases.

CONCLUSION

In this study, we further elucidated the mutational landscape of R/PR AML and revealed potentially actionable mutations in *CSF1R* and *ARID1A*. In addition, we detected recurrent alterations in *UBTF* and *MGA*, solely found in children and adults, respectively. Future studies incorporating various multi-omics analyses are, however, necessary to fully understand this complex disease.

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