The landscape of genotype-phenotype correlation in AML

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Background

- Acute myeloid leukemia (AML) is a group of clinically heterogeneous diseases.
- Heterogeneous presentation of AML is defined by the equally heterogeneous genetic basis during leukemogenesis.

Objective

- To describe the distinct mutation landscape based on the ontogeny of AML.
- To describe the correlation between clinical phenotype and genotype in AML.

Methods

- Bone marrow samples from 536 AML patients were analyzed by targeted capture exome sequencing of 295 genes (N=419) or whole exome sequencing (N=117).
- Extensive clinical-genotype correlation was performed using well annotated clinical data.

Results

Table1. Patient Characteristics

Characteristics	Median	IQR
WBC	5.4	2.2-21.9
HGB	9.3	8.4-10.3
PLT	46	24-92
BM blast %	46	26-72
PB blast %	3	0-18
LDH	715	512-1222
Ferritin	842	442-1847
Age	62	51-72

Characteristics	No.	%
Diagnosis		
de-novo / secondary/Tx-related AML	408/128	76/24
Prior therapy		
untreated / relapse/refractory	411/125	77/23
Cytogenetic risk, ELN defined		
favorable/intermediate/adverse	10/326/177	2/61/33
Induction chemotherapy (previously untreated patients only)		
High intensity chemotherapy (Ida + AraC-based)	204	50
Low intensity chemotherapy (low dose AraC-based)	86	21
Hypomethylating agents	91	22

Figure 1. Landscape of driver mutations

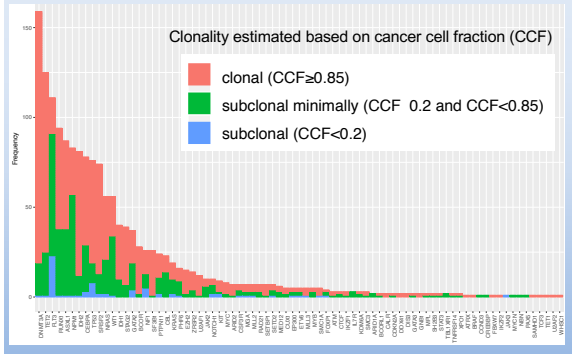


Figure 2. Distinct patterns of somatic mutations based on the ontogeny of AML

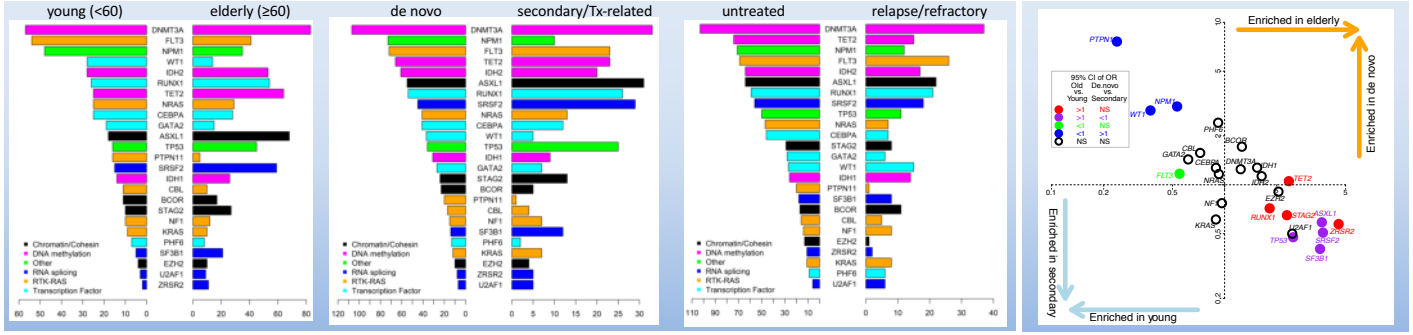


Figure 3. Correlation between somatic mutations and clinical phenotype (BM morphology, PB count, karyotype, immunophenotype based on flow cytometry)

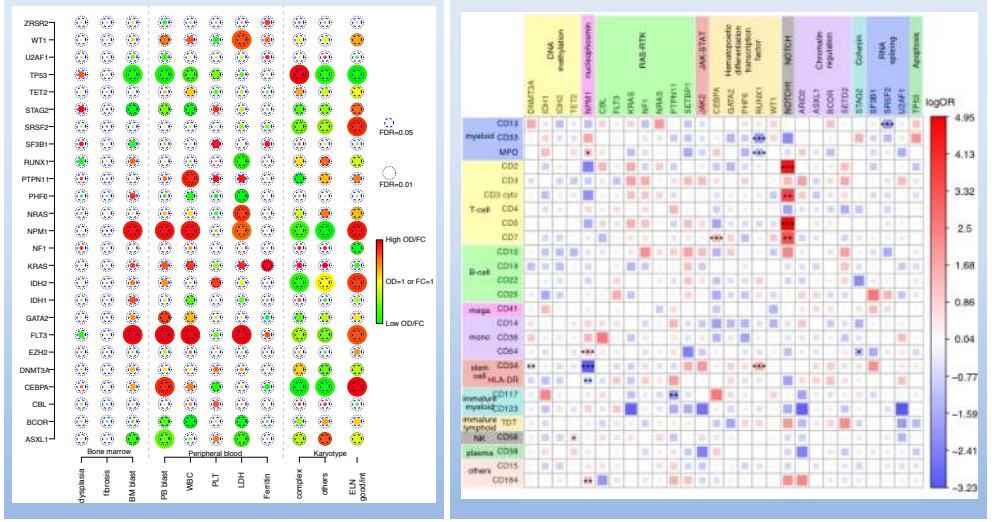
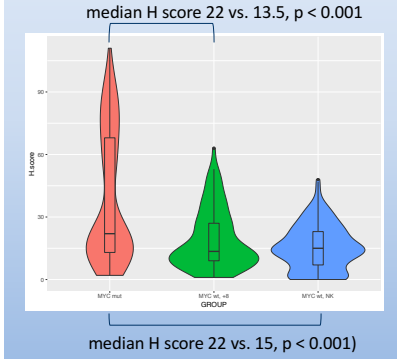


Figure 4. Increased MYC expression in patients with *MYC* mutations

- We detected rare mutations in *MYC* (8 hotspot SNV in exon 2 and 1 ITD) and *MYCN* (1 SNV) in 9 (2%) patients.
- Patients with *MYC* mutation showed significantly higher MYC expression than those without by immunohistochemistry staining.



Conclusions

- We identified significant association between mutations and certain clinical phenotype.
- Class 1 mutations (*NPM1, FLT3, PTPN11, NRAS*) were associated with proliferative disease (high WBC, blast, LDH), whereas patients with mutations in *TP53, STAG2, BCOR*, and *ASXL1* had non-proliferative disease.
- *IDH1, IDH2*, and *NPM1* mutations were associated with decreased expression of HLA-DR. Mutations associated with NOTCH or RAS-RTK pathway showed increased expression of T-cell markers, whereas mutations associated with hematopoietic differentiation transcription factor showed decreased expression of myeloid markers.
- *MYC* mutations were associated with MYC protein overexpression in AML.