Genome Data Allow in silico Pharmacogenetic Studies Using the Genetic Makeup of Both the Individual Patient as well as the Disease

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Background

Understanding the association between the genetic background of a patient and the response to a tailored treatment would strongly influence the choice of therapy and reduce trial-and-error strategies. In the era of genome data, in silico analyses are becoming an interesting tool and the hope is growing to predict a patient's response to therapy by association studies using the genetic makeup of both, the individual patient as well as the disease.

Aim

The aim of this study was to get insights into the genetic background of AML patients refractory to treatment and to investigate associations of polymorphisms (SNPs) in cancer treatment target genes and disease associated mutations contributing to an altered response to treatment.

Patients and Methods

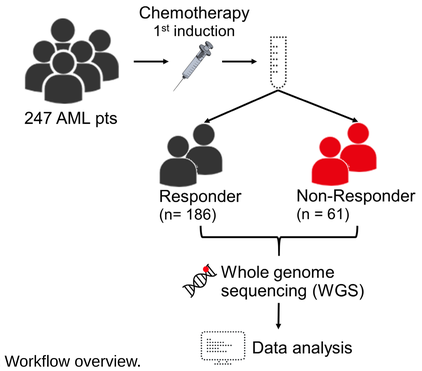

Figure 1: Workflow overview.

247 AML patients (pts) diagnosed by cytomorphology following the WHO classification. All patients were treated intensively with a standard chemotherapy protocol such as 7+3. Following ELN guidelines (Döhner et al., 2017) patients were grouped into responder (group 1), showing cytomorphological complete remission (n=186), or treatment failure (group 2) with only partial remission or progressive disease (n=61). Whole genome sequencing (WGS) was performed with 90x coverage for all samples from diagnosis (Figure 1).

Results

Subtype distribution and mutational profile

Analysis of WGS data was restricted to exonic SNPs of 217 drug target genes (DrugBank 5; Schärfe et al., 2017) associated with cancer treatments and 20 recurrently mutated genes in AML. Morphologic subtypes (Figure 2A) as well as mutation frequencies in AML genes (Figure 2B) were comparable between both groups.

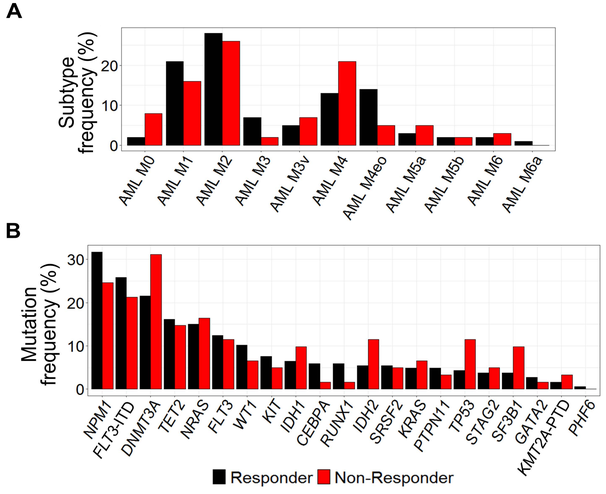

Figure 2: Comparison between the responder and non-responder group regarding morphologic subtypes (A) and mutation frequencies in AML related genes (B).

SNP profiling

In total 9,742 unique SNPs were found with a median of 1,603 per patient. 37% of these SNPs were found in single patients only and another 27% were found in less than 5% of the cases (Figure 3).

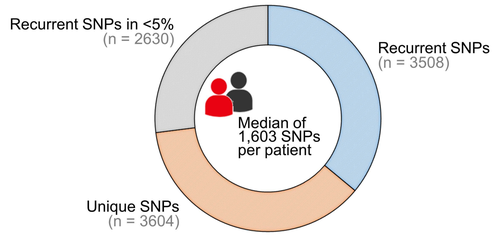

Figure 3: SNP profiling overview.

Co-occurrences of SNPs and somatic variants

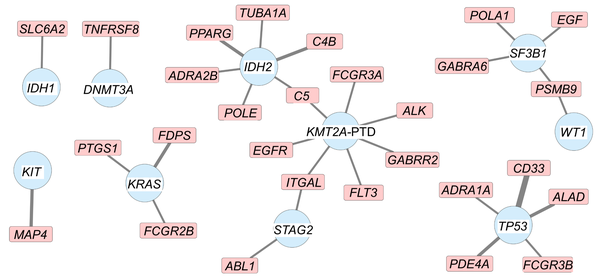

Figure 4: Co-occurrence network of recurrent combinations of somatic variants and missense germline variants in the non-responder group.

Considerably less co-occurrences could be found in the responder group compared to the non-responder group. All identified co-occurrences in group 1 were unique whereas 772 co-occurrences could be found in more than one patient in group 2 (Figure 4). 51% of the patients from group 2 were involved in these interactions, while group 1 did not show any recurrent co-occurrences. It was interesting to note that *IDH2*, *KMT2A*-PTD, *SF3B1* and *TP53* recurrently co-occurred with multiple missense SNPs.

Association of SNPs and drug target genes

The evaluation of potential associations of two SNPs in the investigated drug target genes revealed again the heterogeneity of group 1. Focusing on SNP co-occurrences in at least 10% of the patients showed no hits in group 1, whereas six SNP pairs were found in group 2 (Figure 5A).

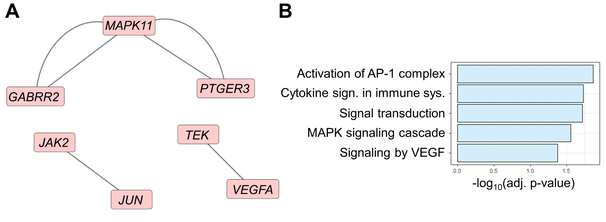

Figure 5: SNP co-occurrences. A) SNP pairs of drug target genes that occurred in at least 10% of the patients in the non-responder group. B) Functional annotation of the genes. Sign: signaling; sys: system

The SNP pairs were tested for enrichment of REACTOME pathways (Fabregat et al. 2018) with PANTHER (Mi et al. 2019). The enrichment revealed a significant association of the SNP pairs with MAPK family signaling cascades (Figure 5B).

Identification of miR-SNPs in drug target genes

Multiple non-coding SNPs were found in the 3'UTR of the drug target genes. These variants showed a higher frequency in group 2 compared to group 1. SNPs in the 3'UTR region might modify mRNA – miRNA interactions by creating, abolishing, or changing the miRNA-binding sites. Recently multiple miR-SNPs have been described that were prognostic for treatment outcome, suggesting a potential as predictive biomarkers.

Conclusion

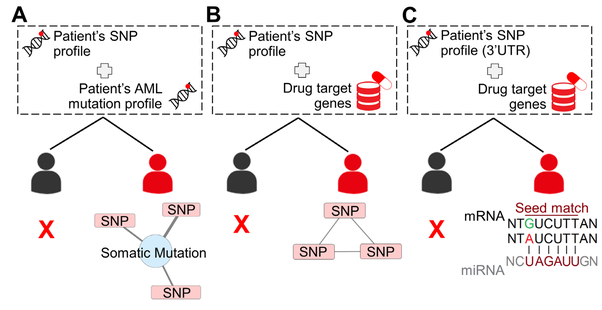

Figure 6: Summary figure of the identified mechanisms as listed in conclusions.

We found three different mechanisms in the non-responder group that potentially alter treatment sensitivity based on the genetic makeup of individual patients:

1) **Association of somatic mutations and SNPs located in drug target genes (Figure 6A)**
2) **Association of two SNPs (Figure 6B)**
3) **SNPs in the 3'UTR modulating miRNA interaction (Figure 6C)**

Disclosures: MM, WW, SH, CB: Employment by MLL Munich Leukemia Laboratory; CH, WK, TH: Equity ownership of MLL Munich Leukemia Laboratory