Comprehensive Whole Genome Sequencing (WGS) Assay Provides Diagnostic Insight into Clinically Relevant Genomic Alterations Across Myeloid Malignancies

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INTRODUCTION

Identification of NCCN and WHO guideline-indicated genetic variation is crucial for diagnosis, risk assessment, and therapeutic decision-making in patients with myeloid malignancies. Here, we report the performance of a WGS assay on patients with acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), myelodysplastic syndromes (MDS) and a small cohort of other hematological malignancies (HM). We show high concordance with matched findings from a DNA-seq panel (Tempus xT), whole transcriptome RNA-seq assay (Tempus xR) , and available cytogenetic results.

METHODS

Our study cohort included 230 clinical samples sequenced from either blood or bone marrow (BM) with a mix of histologies (Figure 1). All 230 samples had results from a targeted-DNA panel, 215 had RNA-seq results, and 10 had cytogenetic data.

For the WGS assay, DNA was used to construct paired-end libraries via tagmentation and WGS to 80X mean coverage with the Illumina NovaSeq-X platform. Data were analyzed using the DRAGEN Platform with custom post-processing filters. We filtered SNV/Indel alterations to 40 genes with VAF>=10%, 608 recurrent rearrangements, and CNAs >5MB.

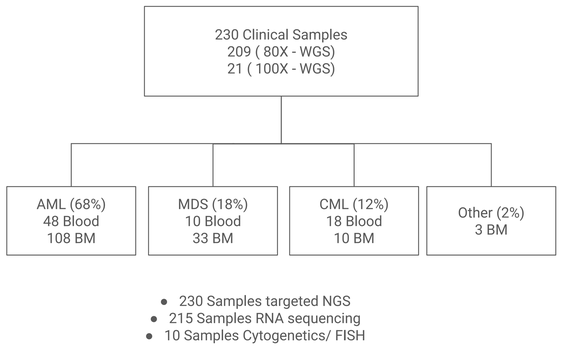

Figure 1. AML/MDS development study setup and summary. Retrospective case-only study design (N=230), utilizing a cohort with established genomic results to assess result replication using our internal process.

SUMMARY

- We demonstrate high concordance (97%) between our WGS assay and conventional methods in identifying guideline recommended genomic alterations, including large CNAs, in myeloid malignancies.
- WGS can identify unique SVs that may be missed by conventional methods and may enhance personalized treatment strategies.

RESULTS

Overall concordance landscape of WGS findings

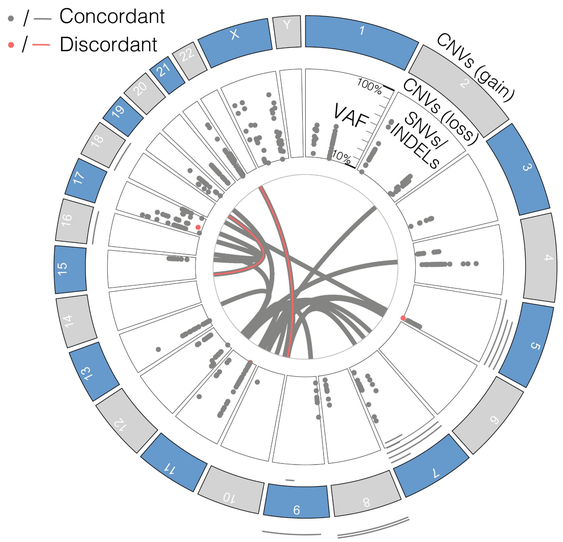

Figure 2. Depiction of observed mutations according to chromosome location. The inner circle depicts SVs detected by WGS (n=119; concordant SVs shown as grey lines, discordant as red lines lines). The middle circles depict SNV/INDELs (n=504). Grey and red dots/lines indicate concordant and discordant results, respectively. The lines adjacent to the chromosome labels depicts locations of only the observed CNVs (losses are inside and gains are outside the chromosome labels) that were concordant with known cytogenetics.

Breakdown of SV detection and concordance according to different assays

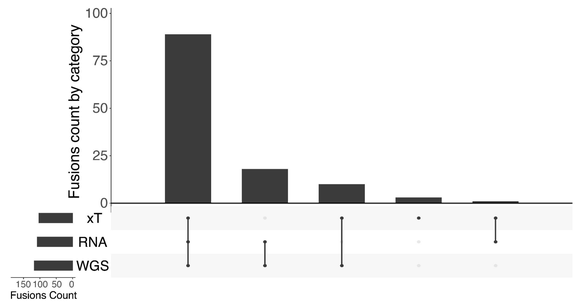

Figure 3. Concordance between WGS and targeted sequencing panel (xT) was 95%. Structural variants (SVs) missed by WGS but identified by xT where detected in regions with >1000x coverage, indicating clonal nature of the alteration and exceeds the 80x coverage typically achieved in WGS.

FLT3 SNVs and internal tandem duplications (ITD)s

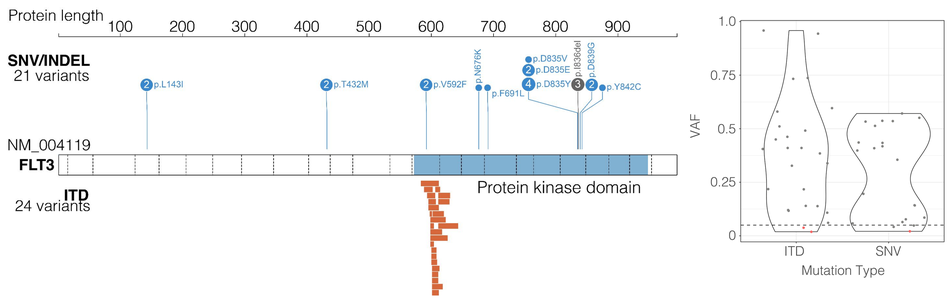

Figure 4. The cohort included 22 SNVs and 26 internal tandem duplications (ITDs) in FLT3, ranging from 12 to 97 nucleotides in length. Of these, 24 ITDs were identified by WGS. Missed ITDs (red dots in the right plot with VAFs from targeted sequencing assay) had VAFs <4% in the xT-Heme assay (dotted line at 5% VAF). WGS showed reduced sensitivity at low VAFs (~600x targeted targeted sequencing depth) likely due to subclonality.

WGS demonstrates 97% concordance with conventional methods in clinical samples

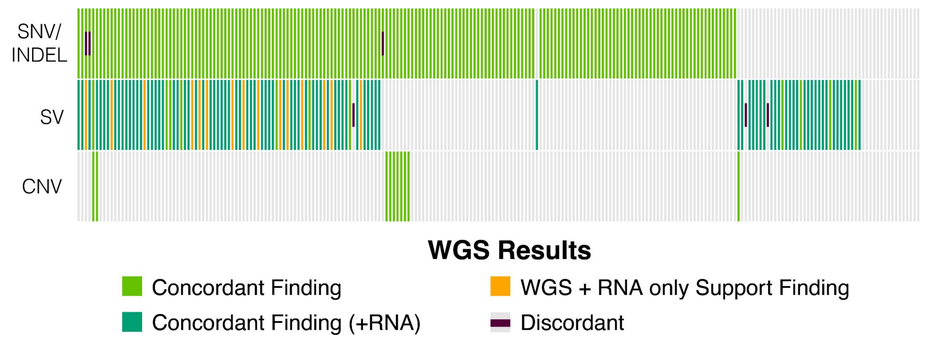

Figure 5. High concordance (97%) was observed between our WGS assay and conventional methods in identifying guideline-recommended genomic alterations. Discordances in SNV/Indels and SV are due to alterations with very low VAFs and high coverage based on targeted sequencing.

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