Myeloid Malignancies Mutation Panel by Next Generation Sequencing

Patient: [redacted]
DOB: [redacted] Age: N/A Gender: U
[redacted]
Patient Identifiers: [redacted]

Visit Number (FIN): [redacted]

Client: [redacted]

Physician: [redacted]

ARUP Test Code: 2011117

Collection Date: 10/28/2021
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Completion Date: 11/03/2021

Comment:

Submitted diagnosis or diagnosis under consideration for variant interpretation: Myelodysplastic syndrome, unspecified

TIER 1: Variants of Known Clinical Significance in Hematologic Malignancies

Gene	Transcript ID	DNA Variant	Protein Variant	Variant Frequency
SF3B1	NM_012433.3	c.2098A>G	p.Lys700Glu	30.9%

TIER 2: Variants of Unknown Clinical Significance in Hematologic Malignancies

Gene	Transcript ID	DNA Variant	Protein Variant	Variant Frequency
SETBP1	NM_015559.2	c.2717C>T	p.Pro906Leu	49.3%

Interpretation

SF3B1 c.2098A>G - SF3B1 encodes a component of the RNA splicing machinery known as the spliceosome. Somatic mutations of SF3B1 are found in 62-82% of patients with myelodysplastic syndrome with ring sideroblasts (MDS-RS) (4) (5) (8) (11) (13) (14) (15). This particular missense mutation has been reported in myeloid malignancies (5) (10) (11). In MDS, some studies have found no independent prognostic value associated with SF3B1 mutations (1) (5) (11); while others have found that MDS patients with SF3B1 mutations have fewer cytopenias, lower risk of progression to acute myeloid leukemia (AML), and longer event-free survival and overall survival than those without SF3B1 mutations (9) (10). Several studies have concluded that SF3B1-mutated MDS is a distinct disease entity with favorable prognosis, regardless of morphological classification (7) (8).

SETBP1 c.2717C>T - SETBP1 encodes a protein that binds to the histone acetylation regulatory protein SET. Somatic mutations of SETBP1 are found in 2-3% of patients with MDS (2) (3) (12). SETBP1 mutations are often gain-of-function mutations clustered in the SKI homologous region. This particular missense variant alters a highly conserved amino acid and has only been reported once in hematologic malignancies (6), to the best of our knowledge. Its functional consequences are unknown. In addition, this variant is listed in the dbSNP database (rs144966931) and is reported in 17 people in the Genome Aggregation Database with a minor allele frequency (MAF) of 0.00006. Given that the variant frequency is close to 50%, it is unclear whether this is a germline or somatic variant. The clinical significance, if any, is uncertain.

Low Coverage Regions

Listed below are regions where the average sequencing depth (number of times a particular nucleotide is sequenced) in at least 20% of the region-of-interest is less than our stringent cutoff of 300. Sensitivity for detection of low allelic frequency variants may be reduced in areas with reduced depth of coverage.

KMT2A(NM_001197104.1) exon 1

STAG2(NM_001042749.2) exon 10

STAG2(NM_001042749.2) exon 4 intron 3

This result has been reviewed and approved by [redacted]

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BACKGROUND INFORMATION: Myeloid Malignancies Panel Interp

CHARACTERISTICS: Myeloid malignancies are clonal disorders of hematopoietic stem and progenitor cells that include myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), myelodysplastic/myeloproliferative neoplasms (MDS/MPN), and acute myeloid leukemia (AML). Recent studies have identified recurrently mutated genes with diagnostic and/or prognostic impact in myeloid malignancies. The presence of certain mutations may inform clinical management. This multi-gene panel by massively parallel sequencing (next generation sequencing) is a more cost-effective approach when compared to the cost of multiple single gene tests. This test can be used to complement the morphologic and cytogenetic workup of myeloid malignancies.
GENES TESTED: ANKRD26, ASXL1, ASXL2, BCOR, BCORL1, BRAF, CALR, CBL, CBLB, CEBPA, CSF3R, CUX1*, DDX41, DNMT1*, DNMT3A, ELANE, ETNK1, ETV6, EZH2, FBXW7, FLT3, GATA1, GATA2, GNAS, HNRNPK,

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IDH1, IDH2, IL7R, JAK1, JAK2, JAK3, KDM6A*, KIT, KMT2A, KRAS, LUC7L2, MPL, NOTCH1, NPM1*, NRAS, NSD1, PHF6, PIGA, PRPF40B, PRPF8, PTPN11, RAD21, RUNX1, SAMD9, SAMD9L, SETBP1, SF3B1, SH2B3, SMC1A, SMC3, SRSF2, STAG2, STAT3, STAT5B*, SUZ12*, TET2, TP53, U2AF1, U2AF2, WT1, ZRSR2.
* - One or more exons of the preferred transcript were not covered by sequencing for the indicated gene; see limitations section below.
METHODOLOGY: Genomic DNA was isolated from peripheral blood or bone marrow and then enriched for the targeted exonic regions of the tested genes. The variant status of the targeted genes was determined by massively parallel sequencing. The hg19 (GRCh37) human genome assembly was used as a reference for identifying genetic variants.
LIMITATIONS: Variants outside the targeted regions or below the limit of detection are not identified. Variants in regions that are not included in the preferred transcript for the targeted genes are not detected. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes or in repetitive or homologous regions. It is also possible some insertion/deletion variants may not be identified. The following regions were not sequenced due to technical limitations of the assay:
CUX1 (NM_181552) exon 24
DNMT1 (NM_001130823) exon 5
KDM6A (NM_001291415) exon 13
NPM1 (NM_002520) exon 1
STAT5B (NM_012448) exons 6-9
SUZ12 (NM_015355) exons 1-9
LIMIT OF DETECTION (LOD): 5 percent variant allele fraction (VAF) for single nucleotide variants (SNV) and small variants less than 24 base pairs (bp). Variants greater than 24bp may be detected at LOD, but the analytical sensitivity may be reduced.
ANALYTICAL SENSITIVITY: The positive percent agreement (PPA) estimate for the respective variant classes (with 95 percent credibility region) are listed below. Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.
Single nucleotide variants (SNVs): 96.9 percent (95.1 98.1 percent)
Insertions/Duplications (1-24bp): 98.1 percent (95.5 99.3 percent)
Insertions/Duplications (greater than 24bp): > 99 percent (92.9 - 100.0 percent)
Deletions (1-24bp): 96.7 percent (92.8 - 98.7 percent)
Deletions (greater than 24bp): 90 percent (79.5 - 96.1 percent)
Multi-nucleotide variants (MNVs): 97 percent (93.0 99.0 percent)
FLT3 ITDs: Greater than 99 percent (97.1 - 100.0 percent)

CLINICAL DISCLAIMER: Results of this test must always be interpreted within the context of clinical findings and other relevant data and should not be used alone for a diagnosis of malignancy. This test is not intended to detect minimal residual disease.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

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