Myeloid Malignancies Mutation Panel by Next Generation Sequencing
ARUP test code 2011117

Myeloid Malignancy Proposed Diagnosis | MDS unspec

Myeloid Malignancies Panel Specimen | Whole Blood

Myeloid Malignancies Panel Interp

Submitted diagnosis or diagnosis under consideration for variant interpretation:
Myelodysplastic syndrome, unspecified (MDS, unspec)

Result:
I. Tier 1 Variants (Variants of known significance in myeloid malignancies):

1. FLT3 c.1780-1800dup, p.Phe594_Asp600dup (NM_004119.2)
   Variant Frequency: 52% (The FLT3-ITD variant frequency by next generation sequencing should not be used as a substitute for a FLT3-ITD allelic ratio. For allelic ratio testing please refer to ARUP test: 2011806)
   Interpretation: The FLT3 gene encodes a receptor tyrosine kinase involved in regulating the development of hematopoietic stem cells (Small, 2006). This variant is a FLT3-Internal tandem duplication (FLT3-ITD). FLT3-ITD mutations occur in the juxtamembrane domain and are found in 20-30% of acute myeloid leukemia (AML) patients (Gilliland and Griffin, 2002; Patel et al., 2012; Thiede et al., 2002). AML patients with FLT3-ITD mutations have a worse outcome (shorter overall survival and higher relapse risk) compared to patients without FLT3-ITD mutations (Gilliland and Griffin, 2002; How et al., 2012; Pratcorona et al., 2013). The prognostic value of FLT3-ITD mutations in AML patients also depends on the mutation status of other prognostic markers (How et al., 2012; Patel et al., 2012; Pratcorona et al., 2013; Pratz et al., 2010). A more recent study showed that AML patients with mutated NPM1 and FLT3-ITD without mutated DNMT3A had a better outcome compared to patients with mutated DNMT3A, NPM1 and FLT3-ITD (Papaemmanuil et al., 2016). A meta-analysis showed that patients with FLT3-ITD and NPM1 mutations (as seen here) have improved complete remission, disease-free survival, and overall survival compared with those who only have FLT3-ITD (Liu et al., 2014). One study found that FLT3 mutations predicted shorter progression-free survival in myelodysplastic syndrome (MDS) patients (Bains et al., 2011). However, another study concluded that FLT3 mutations did not appear to predict poor outcome in patients with MDS (Daver et al., 2011).

2. NPM1 c.860_863dup, p.Trp288fs (NM_002520.6)
   Variant Frequency: 21.4%

H—high  L—low  *—abnormal  C—critical
Interpretation: The NPM1 gene encodes a phosphoprotein that is involved in diverse cellular processes including ribosome biogenesis, maintaining genomic stability, epigenetics, cell proliferation, and programmed cell death (Grisendi et al., 2006). Somatic mutations of NPM1 are found in 22-28% of patients with de novo AML (Courville et al., 2013; Papaemmanuil et al., 2016) with a higher incidence (50-60%) in cyto genetically normal AML (Falini et al., 2009). Somatic mutations of NPM1 are relatively rare in MDS (1.5-5.2%), and appear to be more prevalent (approximately 9%) after leukemic transformation of MDS (Bains et al., 2011; Dicker et al., 2010; Zhang et al., 2007). This particular NPM1 variant (c.860_863dup, p.Trp288fs) is a type A NPM1 exon 11 (formerly known as exon 12) mutation (Ivey et al., 2016) commonly found in AML patients (Caudill et al., 2006; Oppliger Leibundgut et al., 2013). NPM1 mutations are associated with favorable prognosis in AML patients who do not have FLT3-internal tandem duplication (FLT3-ITD) mutations (Falini et al., 2009; Papaemmanuil et al., 2016; Schnittger et al., 2011). One study found that NPM1-positive/FLT3-ITD-negative genotype predicts favorable outcomes in AML patients younger than 65 years but not in those older than 65 years (Ostromoff et al., 2013). A meta-analysis showed that patients with FLT3-ITD and NPM1 mutations (as seen here) have improved complete remission, disease free survival, and overall survival compared with those who only have FLT3-ITD (Liu et al., 2014).

II. Tier 2 Variants (Variants of unknown significance in myeloid malignancies):

1. STAG2 c.1120A>G, p.Arg374Gly (NM_001042749.2) Variant Frequency: 77.3%

Interpretation: STAG2 is a subunit of the cohesin complex which is composed of four core subunits - SMC1A, SMC3, RAD21 and STAG2. Collectively, acquired cohesin complex mutations are found in 8-13% of MDS patients and in 12-14% of AML patients (Cancer Genome Atlas Research, 2013; Kon et al., 2013; Thota et al., 2014). Mutations in cohesin genes are generally mutually exclusive in myeloid malignancies (Thol et al., 2014; Thota et al., 2014). In myeloid malignancies, STAG2 mutations are mostly nonsense, frame-shift and splice site mutations; while STAG2 missense variants are less common (Thota et al., 2014). This particular STAG2 missense variant (p.Arg374Gly) has not been reported in myeloid malignancies or the population databases, to the best of our knowledge. The functional consequences are unknown. Please note that the variant allele frequency is high at 77.3% in this male patient, reflecting the gene is on the X chromosome.

References:


Low coverage regions.
This list contains exons where the average sequencing depth (number of times a particular position is sequenced) is below our stringent cutoff of 500. The sequencing reads from these exons were manually reviewed and the overall sequencing quality is adequate. If variants are detected in these regions they will be listed above in Tier 1 or Tier 2.

This result has been reviewed and approved by Anna Matynia, M.D.
BACKGROUND INFORMATION: Myeloid Malignancies Somatic Mutation and Copy Number Analysis Panel

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 a number of recurrently mutated genes with diagnostic and/or prognostic impact in myeloid malignancies. The presence of certain somatic mutations may also guide treatment selection. This targeted mutation 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: ASXL1, ASXL2, BCOR, BCORL1, BRAF, BRIP1, CALR, CBL, CEBPA, CSF3R, DNMT1, DNMT3A, EED, ELANE, ETNK1, ETV6, EZH2, FLT3, GATA1, GATA2, HRNRNK, IDH1, IDH2, JAK2, JAK3, KDM6A, KIT, KMT2A, KRAS, LUC7L2, MAP2K1, MPL, NOTCH1, NPM1, NRAS, NSD1, P personalised H, PRPF40B, PRPF8, PTPN11, RAD21, RUNX1, SETBP1, SF1, SF3A1, SF3B1, SMC1A, SMC3, SRSF2, SUZ12, TE12, TP53, U2AF1, U2AF2, WT1, ZRSR2.

A full list of the targeted regions of the above genes is available through this link:

METHODOLOGY: Genomic DNA is isolated from peripheral blood or bone marrow and then enriched for the targeted exonic regions of the tested genes. The mutation status of the 57 targeted genes is determined by massively parallel sequencing. The hg19 (GRCh37) human genome assembly is used as a reference for identifying genetic variants.

LIMITATIONS: Mutations outside the targeted regions or below the limit of detection will not be detected. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. It is also possible some insertion/deletion variants may not be identified.

LIMIT OF DETECTION: 5 percent mutant allele.

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.

See Compliance Statement B: aruplab.com/CS

EER Myeloid Malignancies Panel by NGS

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Accession</th>
<th>Collected</th>
<th>Received</th>
<th>Verified/Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloid Malignancy Proposed Diagnosis</td>
<td>17-108-103124</td>
<td>4/18/2017 9:16:00 AM</td>
<td>4/18/2017 9:32:06 AM</td>
<td>1/1/1900 12:00:00 AM</td>
</tr>
<tr>
<td>Myeloid Malignancies Panel Specimen</td>
<td>17-108-103124</td>
<td>4/18/2017 9:16:00 AM</td>
<td>4/18/2017 9:32:06 AM</td>
<td>1/1/1900 12:00:00 AM</td>
</tr>
<tr>
<td>Myeloid Malignancies Panel Interp</td>
<td>17-108-103124</td>
<td>4/18/2017 9:16:00 AM</td>
<td>4/18/2017 9:32:06 AM</td>
<td>1/1/1900 12:00:00 AM</td>
</tr>
<tr>
<td>EER Myeloid Malignancies Panel by NGS</td>
<td>17-108-103124</td>
<td>4/18/2017 9:16:00 AM</td>
<td>4/18/2017 9:32:06 AM</td>
<td>1/1/1900 12:00:00 AM</td>
</tr>
</tbody>
</table>

H - high  L - low  * - abnormal  C - critical
END OF CHART