

Patient ID SA00167525	Patient Name ATLASAB, NGTCL	Birth Date 1966-04-03	Sex F	Age 58
Order Number SA00167525	Client Order Number SA00167525	Ordering Physician CLIENT,CLIENT	Report Notes	
Account Information C7234570 SQA Manual Account		Collected 03 Apr 2024 11:56		

T-cell Lymphoma, NGS, V

Specimen Type

Peripheral blood

MCR

Indication for Test

NA

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Pathogenic Mutations Detected

1. STAT3: Chr17(GRCh37):g.40474482T>A;
NM_139276.2(STAT3):c.1919A>T; p.Tyr640Phe (30%)

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No other pathogenic mutations were detected in the other genes tested on the panel. See below for Variants of Unknown Significance and Additional Information. Please see the section of "Panel Gene List" below for the complete list of genes tested.

Interpretation

1. STAT3: Chr17(GRCh37):g.40474482T>A;
NM_139276.2(STAT3):c.1919A>T; p.Tyr640Phe (30%)

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Normal Gene/Protein Function: The STAT3 gene, located on chromosome 17q21.2, encodes the transcription factor signal transducer and activator of transcription 3 (STAT3). It can be activated by multiple cytokines and growth factors and in its phosphorylated or non-phosphorylated homo/heterodimerized forms, translocate to the nucleus and controls cellular development, differentiation, apoptosis, immune response, and metabolism through transcription regulation of various target genes (Siveen et al., 2014, 24388873).

Mutation effect: The Y640F mutation is located in the SH2 domain important for STAT3 activation and dimerization. It is one of the most common STAT3 mutations in T-cell large granular lymphocytic leukemia (T-LGL) and NK-LGL. The Y640F mutant demonstrated a gain of function with increased STAT3 transcriptional activity, cytokine signaling, and DNA hypermethylation in in vitro studies (Koskela et al., 2012, 22591296; Jerez et al., 2012, 22859607; Kim et al., 2021, 34075200).

Disease Associations: Somatic STAT3 mutations are seen in approximately 30–40% of T-cell large granular lymphocytic leukemia (T-LGL) and NK-LGL patients. T-LGL patients with STAT3 mutations present more often with symptomatic disease, neutropenia, and rheumatoid arthritis compared to those without STAT3 mutations (Rajala et al., 2012, 23596048; Koskela et al., 2012, 22591296; Jerez et al., 2012; Shi et al., 2018, 29288042). Although earlier studies did not observe the impact of STAT3 mutations on overall survival, a recent study reported reduced overall survival in STAT3-mutated LGL patients (Jerez et al., 2012; Barila et al., 2020, 31740810). STAT3 mutations are also reported in approximately 25% of adult T-cell leukemia/lymphoma (ATLL) and more commonly associated with indolent subtype (Bellon et al., 2016, 26813676; Kataoka et al., 2018, 29084771). They have also been described in other T and NK-cell lymphomas, including but are not limited to approximately 90% of breast implant-associated anaplastic large cell lymphoma (ALCL) (Biomberg et al., 2018, 30546832), 10% of ALK-negative ALCL and 5% of cutaneous ALCL (Crescenzo et al., 2015, 25873174), 9% of hepatosplenic T-cell lymphoma (McKinney et al., 2017, 28122867; Nicolae et al., 2014, 24947020), 6% NK/T-cell lymphoma (Kucuk et al., 2015, 25586472), and 16% of enteropathy-associated T-cell lymphoma (EATL) (Moffitt et al., 2017, 28424246). The independent prognostic impact of STAT3 mutations in these diseases is currently elusive.

Performing Site Legend

Code	Laboratory	Address	Lab Director	CLIA Certificate
MCR	Mayo Clinic Laboratories - Rochester Main Campus	200 First Street SW, Rochester, MN 55905	William G. Morice M.D. Ph.D	24D0404292

Patient ID SA00167525	Patient Name ATLASAB, NGTCL	Birth Date 1966-04-03	Sex F	Age 58
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Variants of Unknown Significance

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None.

The VUS variants listed here (with approximate variant allele %) are not sufficiently characterized in the current literature and therefore are of uncertain or unknown clinical significance at this time. They are reported here for future reference in the event they become clinically significant in light of new scientific data.

Additional Information

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None.

Clinical Trials

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Information regarding possible clinical trials for this patient can be found at the following sites:

- 1). ClinicalTrials.gov:
<http://clinicaltrials.gov/ct2/search/advanced>
- 2). Mayo Clinic:
<http://www.mayo.edu/research/clinical-trials>
- 3). National Cancer Institute:
<http://www.cancer.gov/clinicaltrials/search>
- 4). The Leukemia and Lymphoma Society's Clinical Trial Support Center: <https://www.hematology.org/education/clinicians/clinical-trial-support-center>

Method Summary

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A portion of the testing process was performed at Mayo Clinic Laboratories site.

DNA is extracted from validated specimen sources. Library preparation for Next Generation Sequencing (NGS) is performed followed by probe hybridization and capture. Sequencing of the final sample library is performed on a NGS instrument. Following bioinformatic processing of the sequencing data, the sequencing results are interpreted to provide a final clinical report. Genomic alterations are called according to human genome reference build GRCh37 (hg19).

Performance characteristics of NGS panel:

Single base substitutions: accuracy >99%; reproducibility >99% (intra- and interassay); sensitivity 5% variant allele fraction with a minimum depth of coverage of 500X.

Insertion/deletion events (less than or equal to 1000 bps in size): accuracy 100%; reproducibility >99% (intra- and interassay); sensitivity 5% variant allele fraction with a minimum depth of coverage of 500X. Some genetic or genomic alterations such as very large insertion/deletion events, copy number alterations (CNA) and gene translocation events are not detected by this assay.

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Disclaimer
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CLINICAL DISCLAIMER

Mutation calls detected between 5–10% variant allele fractions (VAF) may indicate low-level (i.e. subclonal) tumor populations, although the clinical significance of these findings may not be clear. Some apparent mutations classified as VUS may represent rare or low frequency polymorphisms. Prior treatment for hematologic malignancy could affect the results obtained in this assay. In particular, prior allogeneic hematopoietic stem cell transplant (HSCT) may cause difficulties in resolving somatic or polymorphic alterations, or in assigning variant calls correctly to donor and recipient fractions, if pertinent clinical or laboratory information (e.g. chimerism engraftment status) is not provided. Multiple additional factors may also impact the observed VAF including copy number alterations of the genetic locus, chromosome ploidy changes or subclonal composition. Correlation with clinical, histopathologic and additional laboratory findings is required for final interpretation of these results. This assay does not distinguish between somatic and germline alterations in analyzed gene regions, particularly with VAF near 50% or 100%. If nucleotide alterations in genes associated with germline mutation syndromes are present and there is also a strong clinical suspicion or family history of malignant disease predisposition, additional genetic testing and appropriate counseling may be indicated. This report interpretation is based on current medical and scientific literature, but clinical significance may not be completely established for all reported target gene abnormalities identified. The final interpretation of results for clinical management of the patient is the responsibility of the managing physician. At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that have been previously detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

TECHNICAL DISCLAIMER

The depth of sequencing coverage may be variable for some target regions, but assay performance below the minimum acceptable criteria, or for failed regions is noted. Analysis of rare (low allele frequency) polymorphisms may be problematic in some cases. A low tumor cell percentage in the sample may affect the true mutation VAF and/or sensitivity. Suboptimal-performing regions (i.e. less than the expected minimum depth of coverage) may affect analytic sensitivity for detecting lower level mutations. In the rare event of suboptimal measured DNA input quantity for library preparation (e.g. due to limited tissue amount), detection sensitivity for subclonal variants near the assay limit of detection may be decreased, despite the presence of otherwise acceptable sequencing quality metrics. This is a qualitative test. The variant read fractions are provided for information only and represent a relative proportion of mutated alleles, but do not indicate a measure of analytical sensitivity for the given genes; assay sensitivity is as stated in the method summary. Some genetic or genomic alterations, such as very large insertion/deletion events, copy number alterations (CNA) and gene translocation events are not detected by this assay.

Panel Gene List
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ARID1B (NM_001374820.1) Exons 2–20, CCR4 (NM_005508.4) Exon 2, CXCR4 (NM_003467.2) Exons 1–2, DDX3X (NM_001356.4) Exons 1–17, DNMT3A (NM_022552.4) Exons 2–23, EZH2 (NM_004456.4) Exons 2–20, FYN (NM_002037.5) Exons 4–14, IDH1 (NM_005896.3) Exon 4, IDH2 (NM_002168.3) Exon 4, JAK1 (NM_002227.3) Exons 2–25, JAK3 (NM_000215.3) Exons 2–24, KMT2D (NM_003482.3) Exons 1–54, KRAS (NM_033360.3) Exons 2–4, MSC (NM_005098.3) Exons 1–2, NOTCH1 (NM_017617.3) Exons 26–27, 34, NRAS (NM_002524.4) Exons 2–4, PLCG1 (NM_002660.2) Exons 1–32, RHOA (NM_001664.3) Exons 2–3, STAT3 (NM_139276.2) Exons 2–24, STAT5B (NM_012448.3) Exons 14–19, TET2 (NM_001127208.2) Exons 3–11, TP53 (NM_000546.4) Exons 4–11.

For some genes, the transcript IDs used in the analysis may not be the same as in other cancer mutation databases, such as COSMIC <http://cancer.sanger.ac.uk/cosmic>

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Reviewed By

MCR

Signing Pathologist: SHANDA VOELTZ

NGTCL Result

MCR

See Interpretation

Received: 03 Apr 2024 13:33

Reported: 03 Apr 2024 13:47

Laboratory Notes

- 1

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

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