Solid Tumor Mutation Panel by Next Generation Sequencing

Patient: [redacted]
DOB: [redacted] Age: 60 Gender: F
Patient Identifiers: [redacted]

Visit Number (FIN): [redacted]

Client: [redacted]

Physician: [redacted]

ARUP Test Code: 2007991

Collection Date: 06/10/2020
Received in lab: 06/10/2020
Completion Date: 06/22/2020

Comment:

Block ID: 123ABC
Clinical History: Melanoma
Sample Source: Skin

TIER 1: Variants of Strong Clinical Significance

Variants with therapeutic, diagnostic, or prognostic significance in the patients specific tumor type

Gene	Transcript ID	DNA Variant	Protein Variant
KIT	NM_000222.2	c.1648_1677del	p.Lys550_Val559del

Interpretation

KIT - The KIT gene encodes a receptor tyrosine kinase that is involved in signaling associated with cell survival, proliferation, and differentiation (5). Somatic KIT mutations are found in 2-8% of patients with malignant melanoma and are more commonly found in those with mucosal melanomas (15-39%) (1) (4) (12). This particular exon 11 KIT mutation (p.Lys550_Val559del) within the juxtamembrane domain is a recurrent mutation in melanoma (3). Activating KIT mutations may predict response to tyrosine kinase inhibitors (11).

TIER 2: Variants of Potential Clinical Significance

Variants with therapeutic, diagnostic, or prognostic significance in another tumor type

Gene	Transcript ID	DNA Variant	Protein Variant
TERT	NM_198253.2	c.-124C>T	p.?

Interpretation

TERT - The TERT gene encodes the catalytic subunit of telomerase, which regulates telomere length at the ends of chromosomes (7). Somatic TERT promoter mutations are found in 29-38% of melanomas (7) (10) (13). This particular TERT promoter mutation (c.-124C>T) is presumed to create a novel Ets/TCF binding motif and increase transcriptional activity from the TERT promoter (2) (7) (8). Some studies indicate that melanoma patients with TERT promoter mutations may have both shorter disease-free and overall survival (6) (10). Notably, the effects of a TERT promoter mutation may be modulated by other genetic polymorphisms outside the reportable range of this assay (10).

TIER 3: Variants of Unknown Clinical Significance (VUS)

Gene	Transcript ID	DNA Variant	Protein Variant
MET	NM_001127500.2	c.3029C>T	p.Thr1010Ile

Interpretation

MET - No clinically relevant information was found for this variant.

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 300. The sequencing reads from these exons were manually reviewed. If high quality variants are detected in these regions they will be listed above in Tier 1 or Tier 2.

None

This result has been reviewed and approved by [redacted]

References

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(3) COSMIC: https://cancer.sanger.ac.uk/cosmic

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(5) Edling CE, Hallberg B, c-Kit--a hematopoietic cell essential receptor tyrosine kinase. Int J Biochem Cell Biol 2007. PMID:17350321

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(9) Li MM, Datto M, Duncavage EJ et al, Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn 2017. PMID:27993330

(10) Nagore E, Heidenreich B, Rachakonda S et al, TERT promoter mutations in melanoma survival. Int J Cancer 2016. PMID:26875008

(11) NCCN_melanoma_v3_2020: NCCN Clinical Practice Guidelines in Oncology: Cutaneous Melanoma Version 3.2020 - May 18, 2020: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma_blocks.pdf

(12) Torres-Cabala CA, Wang WL, Trent J et al, Correlation between KIT expression and KIT mutation in melanoma: a study of 173 cases with emphasis on the acral-lentiginous/mucosal type. Mod Pathol 2009. PMID:19718013

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BACKGROUND INFORMATION: Solid Tumor Mutation Panel by Next Generation Sequencing

CHARACTERISTICS: Specific somatic variants have been discovered in multiple cancer-related genes and have diagnostic, therapeutic and/or prognostic utility in several cancer types. Targeted next generation sequencing is utilized in this test for the detection of hotspot variants within 44 cancer-related genes and includes extended RAS variant detection. The personalized variant profile may be useful for prediction of patient diagnosis, prognosis and/or response to targeted therapies in solid tumors including, melanoma, gastrointestinal stromal

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tumors (GIST), colorectal cancers, bladder cancers, and hepatocellular cancers.

GENES TESTED: AKT1, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CTNNB1, DDR2, EGFR, ERBB2, ERBB4, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, GNA11, GNAQ, GNAS, HRAS, IDH1, IDH2, KDR, KIT, KRAS, MAP2K1, MET, MTOR, NOTCH1, NRAS, NTRK1, PDGFRA, PIK3CA, PTEN, RB1, RET, ROS1, SMAD4, SMO, STK11, TERT promoter, TP53, VHL. A full list of targeted regions within the above genes is available through this link: http://ltd.aruplab.com/Tests/Pdf/375.

METHODOLOGY: Genomic DNA is isolated from microscopically-guided dissection of tumor tissue and then enriched for the targeted regions of the tested genes. The variant status of the 44 targeted genes is determined by massively parallel sequencing (next generation sequencing). The hg19 (GRCh37) reference sequence is used as a reference for identifying genetic variants.

LIMITATIONS: This test will not detect variants in areas outside the targeted genomic regions or below the limit of detection. Copy number alterations, translocations, microsatellite instability, and tumor mutational burden will not be detected. If clinical indication is lung cancer, additional clinical evaluation may be considered for complete genetic analysis including, detection of translocations or gene rearrangements. This test is not intended to detect minimal residual disease. This test evaluates for variants in tumor tissue only and cannot distinguish between somatic and germline variants. Therefore, if a hereditary/familial cancer is of clinical concern, consider additional clinical evaluation and genetic counseling prior to additional testing. In some cases, variants may not be identified due to technical limitations in the presence of known pseudogenes, homologous regions and/or low mapability regions. This includes variants in PTEN exons 1, 2, 4, 5, 6, 7, 8 and 9; MAP2K1 exons 2, 7 and 11; CDKN2A exon 2, PIK3CA exons 10 and 14; GNAQ exon 5; EZH2 exon 18; and BRAF exon 11. It is also possible that some large insertion/deletion variants (especially those greater than 60bp) may not be detected. Tissue samples yielding at least 10ng are acceptable but may yield suboptimal results if yield is less than 50ng.

LIMIT OF DETECTION: 5 percent mutant allele for single nucleotide variants (SNV), small to medium sized multi-nucleotide variants (MNV) (less than 60bp).

ANALYTICAL SENSITIVITY (PPA): Analytical sensitivity for all variant classes available through this link: http://ltd.aruplab.com/Tests/Pdf/375.

CLINICAL DISCLAIMER: Results of this test must always be interpreted within the clinical context 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.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement B: aruplab.com/CS