Precision Panel- 50 Genes

Test Description

The MolQ Precision Panel includes 50 genes, involving hotspot regions and 3159 unique variants, applicable to a wide range of tumor types for detection of SNV (single and multiple nucleotide variation), Insertion-Deletion, Copy Number Variation (CNV), and gene Fusions. Fusion and splice variants are detected in RNA.

Patient Demographic

Name: Mr. Abhay Singh
Sex: Male
Date of Birth/Age: 62 years
Disease: Non-Small Cell Lung Carcinoma

Clinician

Clinician Name: Dr Amit Verma
Medical Facility: Dr AV Institute of Personalized Cancer Therapy and Research
Pathologist: Not Provided

Specimen

Booking ID: 012304220236
Sample Type: FFPE
Tumor Content Percentage: 40%
Date of Collection: 21-04-2023
Date of Booking: 21-04-2023

CLINICAL SYNOPSIS

Abhay Singh, is a known case of non-small cell lung carcinoma. He has been evaluated for pathogenic variations in the genes listed in Appendix 2.

RESULT SUMMARY

The assay has detected *NRAS* mutation (p.Gln61Leu, VAF= 56.93%) along with *TP53* (p.Gly245Cys, VAF=23.54%) mutation. There are multiple approved therapies available to target *NRAS* mutation in other cancer types. There are multiple drugs in clinical trial to target these mutations in lung cancers.

Studies suggest *NRAS* mutations potential sensitivity to MEK inhibitors[1]. Recent data shows *NRAS* mutated NSCLC had promising efficacy of immunotherapy in combination with chemotherapy[2]. Hence PDL1 testing is also suggested.

RESULTS

Variants in *TP53* and *NRAS* genes related to the given phenotype were detected.

Gene/ Transcript (Locus)	Variant ID	Variant	Allele Frequency	Variant Effect	*Relevant Therapies (In this cancer type)	*Relevant Therapies (In other cancer type)	Tier[3]
NRAS NM_002524.5 (chr1:115256529)	COSM583	c.182A>T (p.Gln61Leu)	56.93%	Missense	None	anti-CTLA-4 + anti-PD-1 anti-PD-1 bevacizumab + chemotherapy binimetinib	IIc
TP53 NM_000546.5 (chr17:7577548)	COSM11081	c.733G>T (p.Gly245Cys)	23.54%	Missense	None	None	IIc

* Public data sources included in relevant therapies: FDA, NCCN, EMA, ESMO

CLINICAL CORRELATION AND VARIANT INTERPRETATION

NRAS **p.Gln61Leu**

Gene description: The *NRAS* proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the *RAS* superfamily which also includes *KRAS* and *HRAS*. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival[4-6].

Alterations and prevalence: Recurrent mutations in *RAS* oncogenes cause constitutive activation and are found in 20-30% of cancers. *NRAS* mutations are particularly common in melanomas (up to 25%) and are observed at frequencies of 5-10% in acute myeloid leukemia, colorectal, and thyroid cancers[7,8]. The majority of *NRAS* mutations consist of point mutations at G12, G13, and Q61[7,9]. Mutations at A59, K117, and A146 have also been observed but are less frequent[10,11].

Potential relevance: Currently, no therapies are approved for *NRAS* aberrations. The EGFR antagonists, cetuximab[12] and panitumumab[13], are contraindicated for treatment of colorectal cancer patients with *NRAS* mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[11]. The FDA has granted fast track designation to the pan-RAF inhibitor, KIN-2787[14], for the treatment of *NRAS* mutation positive metastatic or unresectable melanoma. *NRAS* mutations are associated with poor prognosis in patients with low-risk myelodysplastic syndrome[15] as well as melanoma[16]. In a phase III clinical trial in patients with advanced NRAS-mutant melanoma, binimetinib improved progression free survival (PFS) relative to dacarbazine with median PFS of 2.8 and 1.5 months, respectively[17].

TP53 **p.Gly245Cys**

Gene description: The *TP53* gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, *TP53* is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in *TP53* is required for oncogenesis as they result in loss of protein function and gain of transforming potential[18]. Germline mutations in *TP53* are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[19,20].

Alterations and prevalence: *TP53* is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing *TP53* mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high *TP53* mutation rates (60-90%)[7,10,21-24]. Approximately two-thirds of *TP53* mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, Y220, R248, R273, and R282[7,10]. Invariably, recurrent missense mutations in *TP53* inactivate its ability to bind DNA and activate transcription of target genes[25-28].

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast-track designation (2020) by the FDA for advanced tumors harboring a *TP53* Y220C mutation[29]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[30] and breakthrough designation[31] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a *TP53* mutation, respectively. In addition to investigational therapies aimed at restoring wild-type *TP53* activity, compounds that induce synthetic lethality are also under clinical evaluation[32,33]. *TP53* mutations confer poor prognosis in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL)[15,34-36]. In mantle cell lymphoma, *TP53* mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[37]. Mono- and bi-allelic mutations in *TP53* confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[38].

RECOMMENDATIONS

- Validation of the variant(s) by Sanger sequencing is recommended to rule out false positives.
- **Sequencing the variant(s) in the other affected and unaffected members of the family is recommended to confirm the significance.**
- Genetic counselling is advised for interpretation on the consequences of the variant(s).
- If results obtained do not match the clinical findings, additional testing should be considered as per referring clinician's recommendations.

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APPENDIX 1: TEST METHODOLOGY

Method

DNA and RNA were extracted from samples using the Qiagen FFPE DNA kit and Promega ReliaPrep FFPE Total RNA Miniprep system. Isolated DNA/RNA was directly loaded on Genexus Next Generation Sequencer and subjected to automated library preparation and template preparation followed by sequencing at average depth of ~4000X.
It utilizes unique molecular tags to enable high sensitivity detection of variants. Analysis is done using Ion Torrent Reporter Software, the data is visualized on Integrative Genomics Viewer (IGV) and analyzed. The final report is generated using Oncomine curated knowledgebase reporter and includes clinical trials information continuously being updated for the best of the patient management as per clinical guidelines.

DISCLAIMER

- This report was generated using the materials and methods as recommended which required the use of quality reagents, protocols, instruments, software, databases and other items, some of which were provided or made accessible by third parties. A defect or malfunction in any such reagents, protocols, instruments, software, databases and/or other items may compromise the quality or accuracy of the report.
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- Medical knowledge and annotation are constantly updated and reflects the current knowledge at the time.
- Due to inherent technology limitations of the assay, not all bases of the exome can be covered by this test. Accordingly, variants in regions of insufficient coverage may not be identified and/or interpreted. Therefore, it is possible that certain variants are present in one or more of the genes analyzed, but have not been detected. The variants not detected by the assay that was performed may/ may not impact the phenotype.
- It is also possible that a pathogenic variant is present in a gene that was not selected for analysis and/or interpretation in cases where insufficient phenotypic information is available.
- The report shall be generated within turnaround time (TAT), however, such TAT may vary depending upon the complexity of test(s) requested. MolQ Laboratory under no circumstances will be liable for any delay beyond afore mentioned TAT.
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- This is a laboratory developed test and the development and the performance characteristics of this test was determined by reference laboratory as required by the CLIA 1988 regulations. The report, and the tests used to generate the Report have not been cleared or approved by the US Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. The test results have scientifically shown to be clinically useful.

APPENDIX 2: GENE LIST WITH COVERAGE

DNA Hotspots					
AKT1	*AKT2*	*AKT3*	*ALK*	*AR*	*ARAF*
BRAF	*CDK4*	*CDKN2A*	*CHEK2*	*CTNNB1*	*EGFR*
ERBB2	*ERBB3*	*ERBB4*	*ESR1*	*FGFR1*	*FGFR2*
FGFR3	*FGFR4*	*FLT3*	*GNA11*	*GNAQ*	*GNAS*
HRAS	*IDH1*	*IDH2*	*KIT*	*KRAS*	*MAPK1*
MAPK2	*MET*	*MTOR*	*NRAS*	*NTRK1*	*NTRK2*
NTRK3	*PDGFRA*	*PIK3CA*	*PTEN*	*RAF1*	*RET*
ROS1	*SMO*	*TP53*			
CNVs					
ALK	*AR*	*CD274*	*CDKN2A*	*EGFR*	*ERBB2*
ERBB3	*FGFR1*	*FGFR2*	*FGFR3*	*KRAS*	*MET*
PIK3CA	*PTEN*				
Inter-genetic Fusions					
ALK	BRAF	*ESR1*	*FGFR1*	*FGFR2*	*FGFR3*
MET	*NRG1*	*NTRK1*	*NTRK2*	*NTRK3*	*NUTM1*
RET	*ROS1*	*RSPO2*	*RSPO3*		
Intra-genetic Fusions					
AR	*EGFR*	*MET*			