Comprehensive Panel- 206 Genes

Test Description

The MolQ Comprehensive Panel includes 206 key solid tumor genes that are well characterized in the published literature and associated with oncology drugs that are FDA approved, part of NCCN guidelines, or in clinical trials. The assay allows concurrent analysis of DNA and RNA in a single workflow involving detection of multiple types of variants, including hotspots, single nucleotide variants (SNVs), indels, CNVs and gene fusions.

Patient Demographic

Name: Ms. Raksha Sharma
Sex: Female
Date of Birth/Age: 69 years
Disease: Myxoid Leiomyosarcoma

Clinician

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

Specimen

Booking ID: 012312110022
Sample Type: FFPE Block No. B-14031/22
Tumor Content Percentage: 50%
Date of Collection: 11-12-2023
Date of Booking: 11-12-2023

CLINICAL SYNOPSIS

Raksha Sharma, is a known case of myxoid leiomyosarcoma. She has been evaluated for pathogenic variations in the genes listed in Appendix 2.

Note: The quality of RNA extraction was insufficient to proceed with the identification of RNA fusions.
Fusion variant identification was performed using DNA fusion calling, no fusions were detected, there may be potential compromise in sensitivity.

RESULTS

Positive for *MDM4* gene amplification.

Gene	Copy No.	Tier[1]
MDM4	6	IId

RELEVANT CANCER SPECIFIC FINDINGS

Gene	Findings (At DNA Level)	Gene	Findings (At DNA Level)
ERBB2	None detected	*PDGFRA*	None detected
KRAS	None detected	*MDM2*	None detected
BRAF	None detected	*CDK4/6*	None detected
KIT	None detected		

CLINICAL CORRELATION AND VARIANT INTERPRETATION

MDM4 **Amplification**

Variant description: *MDM4* (also known as MDMX), encodes a nuclear protein showing structural homology to MDM2. MDM4 can interact with p53, and inhibits its activity via the binding of its transcription activation domain. MDM4 is an oncogene and has been shown to be amplified in a variety of cancer subsets, including retinoblastoma, breast carcinoma, glioblastoma, colorectal carcinoma, or endometrial carcinoma. More recently, *MDM2/MDM4* amplifications have been proposed as predictive markers of primary resistance to immune checkpoint inhibitors in a variety of tumors, even if the precise mechanisms governing their impact on immune response remains to be investigated. Concerning sarcoma, *MDM4* amplification has been reported in one case of dedifferentiated liposarcoma (DDLPS) lacking *MDM2* amplification and in exceptional cases of DDLPS, leiomyosarcoma, myxofibrosarcoma, and undifferentiated pleomorphic sarcoma. MDM4 amplification is an exceptional molecular event alternative to MDM2 amplification in ALT/WDLPS. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with MDM4-amplified myxoid sarcoma.

REFERENCE

Gruel N et al. Genes, Chromosomes and Cancer. 2023

RECOMMENDATION

- Genetic counselling is advised for interpretation on the consequences of the variant(s).

Jatinder Kaur, PhD
Head, Molecular Biology & Genomics

Dr. Gulshan Yadav, MD
Head, Pathology

APPENDIX 1: TEST METHODOLOGY

Method

Massively Parallel Sequencing (Next Generation Sequencing): Tumor Nucleic acid from the submitted specimen was enriched for the coding regions of genes in the panel and splice site junctions of genes. DNA and RNA were extracted from samples using the Qiagen FFPE DNA and RNAeasy FFPE kit. Paired end sequencing was performed on Illumina platform (NovaSeq 6000/NextSeq2000) with a minimum depth of 500X. The assay allows concurrent analysis of DNA and RNA. Assay detect multiple types of variants, including hotspots, single nucleotide variants (SNVs), indels, CNVs, and gene fusions, in a single workflow**.** All positive variants are visualized on Integrative Genomics Viewer (IGV) and reported.

AMP/ASCO/CAP Classification

Tier I: Variants of Strong Clinical Significance	1A	Biomarkers that predict response or resistance to US FDA-approved therapies for a specific type of tumor or have been included in **professional guidelines** as **therapeutic, diagnostic, and/or prognostic biomarkers** for specific types of tumors.
	1B	Biomarkers that predict response or resistance to a therapy based on well-powered studies with consensus from experts in the field, or have diagnostic and/or prognostic significance of certain diseases based on **well- powered studies with expert consensus**.
Tier II: Variants of Potential Clinical Significance	2C	Biomarkers that predict response or resistance to therapies approved by FDA or professional **societies for a different tumor type (ie, off-label use of a drug)**, serve as inclusion criteria for clinical trials, or have diagnostic and/or prognostic significance based on the results of multiple small studies.
	2D	Biomarkers that show plausible therapeutic significance based on preclinical studies, or may assist disease diagnosis and/or prognosis themselves or along with other biomarkers based on **small studies or multiple case reports** with no consensus.
Tier III: Variants of Unknown Clinical Significance		Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases No convincing published evidence of cancer association.
Tier IV: Benign or Likely Benign Variants		Observed at significant allele frequency in the general or specific subpopulation databases.

DISCLAIMER

- Interpretation of variants in this report is performed to the best knowledge of the laboratory based on the information available at the time of reporting. The classification of variants can change over time and MolQ cannot be held responsible for this. Please feel free to contact MolQ Laboratory (contact@molq.in) in the future to determine if there have been any changes in the classification of any variations. Re-analysis of variants in previously issued reports in light of new evidence is not routinely performed, but may be considered upon request, provided the variant is covered in the current panel.
- 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.
- Genes with pseudogenes, paralog genes and genes with low complexity may have decreased sensitivity and specificity of variant detection and interpretation due to inability of the data and analysis tools to unambiguously determine the origin of the sequence data in such regions.
- The mutations have not been validated/confirmed by Sanger sequencing.
- Incidental or secondary findings (if any) that meet the ACMG guidelines can be given upon request.
- 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.
- It is hereby clarified that the report(s) generated from the test(s) do not provide any diagnosis or opinion or recommends any cure in any manner. MolQ Laboratory hereby recommends the patient and/or the guardians of the patients, as the case may be, to take assistance of the clinician or a certified physician or doctor, to interpret the report(s) thus generated. MolQ Laboratory hereby disclaims all liability arising in connection with the report(s).

- In a very few cases genetic test may not show the correct results, e.g. because of the quality of the material provided to MolQ Laboratory. In case where any test provided by MolQ Laboratory fails for unforeseeable or unknown reasons that cannot be influenced by MolQ Laboratory in advance, MolQ Laboratory shall not be responsible for the incomplete, potentially misleading or even wrong result of any testing if such could not be recognized by MolQ Laboratory in advance.
- This is a laboratory developed test and the development and the performance characteristics of this test was determined by reference laboratory.

LIMITATIONS

- Testing has been performed assuming that the sample received belongs to the above-named individual(s) and any stated relationships between individuals are accepted as true.
- Negative (wild type) result does not rule out the presence of a mutation that may be present but below the limits of detection of this assay. The analytical sensitivity of this assay is 5%. Sequencing is performed at a depth of 500x
- This test does not differentiate between somatic and germline alterations. Additional testing may be necessary to clarify the significance of results if there is a potential hereditary risk.
- Due to inherent technology limitations, coverage is not uniform across all regions. Hence pathogenic variants present in areas of insufficient coverage may not be analyzed/ reported.
- The classification and interpretation of all the variants in this assay reflects the current state of scientific understanding at the time this report was issued. In some instances, the classification and interpretation of such variants may change as new scientific information comes to light.
- Test results should be interpreted in context of clinical findings, tumor sampling, histopathology, and other laboratory data.
- If results obtained do not match other clinical laboratory findings, please contact the laboratory for possible. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.
- Genetic testing is highly accurate. Rarely, inaccurate results may occur for various reasons. These reasons include, but are not limited to mislabelled samples, inaccurate reporting of clinical/medical information, rare technical errors or unusual circumstances such as bone marrow transplantation, blood transfusion; or the presence of change(s) in such a small percentage of cells that may not be detectable by the test (mosaicism).

APPENDIX 2: GENE LIST

Gene	Gene	Gene	Gene	Gene	Gene	Gene
ABL1	*CD274*	*EWSR1*	*HRAS*	*MYCN*	*POLE*	*SMARCB1*
ACVR1	*CD74*	*EZHIP*	*IDH1*	*MYH7*	*PPARG*	*SMARCE1*
AKT1	*CDH1*	*FANCA*	*IDH2*	*NAB2*	*PPP2R2A*	*SMO*
AKT2	*CDK12*	*FANCI*	*JAG1*	*NBN*	*PRDM6*	*SS18*
AKT3	*CDK4*	*FANCL*	*JAZF1*	*NCOA2*	*PRKCA*	*SSX1*
ALK	*CDK6*	*FBXW7*	*KDM6A*	*NF1*	*PTCH1*	*SSX2*
APC	*CDKN1B*	*FEV*	*KDR*	*NF2*	*PTEN*	*SSX2B*
AR	*CDKN2A*	*FGFR1*	*KIF5B*	*NOTCH1*	*QKI*	*STAT6*
ARAF	*CDKN2B*	*FGFR2*	*KIT*	*NOTCH2*	*RAD51*	*STK11*
ARID1A	*CHEK1*	*FGFR3*	*KLF4*	*NRAS*	*RAD51B*	*SUFU*
ASPSCR1	*CHEK2*	*FGFR4*	*KMT2A*	*NRG1*	*RAD51C*	*SUZ12*
ATF1	*CREB3L1*	*FH*	*KRAS*	*NTRK1*	*RAD51D*	*TERT*
ATM	*CTNNB1*	*FLCN*	*MAML2*	*NTRK2*	*RAD54L*	*TEX12*
ATP7B	*CYSLTR2*	*FLI1*	*MAP2K1*	*NTRK3*	*RAF1*	*TFE3*
ATR	*DDIT3*	*FLT1*	*MAP2K2*	*NUTM1*	*RARA*	*TFEB*
ATRX	*DDR2*	*FLT3*	*MDM2*	*PALB2*	*RB1*	*TMPRSS2*
BAP1	*DDX3X*	*FLT4*	*MDM4*	*PAX3*	*RELA*	*TOE1*
BARD1	*DICER1*	*FOXL2*	*MEN1*	*PAX7*	*RET*	*TP53*
BCL2	*DNAJB1*	*FOXO1*	*MET*	*PAX8*	*RHEB*	*TPM3*
BCL6	*DPYD*	*FOXR2*	*MGMT*	*PDGFB*	*RICTOR*	*TRAF7*
BCOR	*EGFR*	*FUS*	*MLH1*	*PDGFRA*	*ROS1*	*TSC1*
BCR	*EML4*	*GLI2*	*MN1*	*PDGFRB*	*SDC4*	*TSC2*
BRAF	*EP300*	*GNA11*	*MRE11*	*PGR*	*SDHA*	*VHL*
BRCA1	*EPCAM*	*GNAQ*	*MSH2*	*PIK3CA*	*SDHB*	*WT1*
BRCA2	*ERBB2*	*GNAS*	*MSH6*	*PIK3R1*	*SDHC*	*YAP1*
BRIP1	*ERBB3*	*H3-3A*	*MTOR*	*PKD1*	*SDHD*	*YWHAE*
CCND1	*ERCC2*	*H3C2*	*MUTYH*	*PKHD1*	*SF3B1*	
CCND2	*ERG*	*H3C3*	*MYB*	*PLCB4*	*SLC34A2*	
CCND3	*ESR1*	*HEY1*	*MYC*	*PMS2*	*SMAD4*	
CCNE1	*ETV6*	*HFE*	*MYCL*	*POLD1*	*SMARCA4*	