Multiple Myeloma Panel

Personal Information	Specimen Information	Test Information
Name:	Sample ID: 20220727-971-0000	Test reported: 2022-08-09
Date of Birth:	Medical record No:	Ordering physician:
Sex:	Date received: 2022-07-27	Institution:

Cancer Type R/O Multiple Myeloma

RESULT SUMMARY

	Tier 1	Tier 2	Tier 3
Variant	2	0	3
Gene	TRAF3	-	DIS3, TRAF3

TEST RESULT

Tier 1 : Variants of Strong Clinical Significance 2

No	Gene	DNA	Protein	VAF(%)	Depth(X)	COSMIC ID
1	TRAF3	c.262del	p.Cys88Valfs*41	5	1,429	-
2	TRAF3	c.1623del	p.Val542Phefs*2	2	1,613	-

INTERPRETATION

The c.262del (p.Cys88Valfs*41) variant and c.1623del (p.Val542Phefs*2) variant in the TRAF3 gene have not been previously reported in cancer tissues including hematologic malignancies, but the loss-of-function mutation of the TRAF3 gene is one of the abnormalities commonly found in multiple myeloma. The TRAF3 gene is a kind of tumor suppressor gene and is a negative regulator of the NF-kB pathway, and loss-of-function mutation of the TRAF3 gene causes activation of the NF-kB pathway, resulting in enhanced B-cell survival. The TRAF3 loss-of-function mutation is found in ~20% of multiple myeloma, and the NF-kB pathway abnormalities have been reported to be prognostically neutral (Proc Natl Acad Sci USA 2016;113:1032-7, J Clin Oncol 2015;33: 3911-20).

Tier 2 : Variants of Potential Clinical Significance 0

No	Gene	DNA	Protein	VAF(%)	Depth(X)	COSMIC ID

No variant

INTERPRETATION

No tier 2 (Potential clinical importance) mutations were identified.

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Tier 3 : Variants of Unknown Clinical Significance 3

No	Gene	DNA	Protein	VAF(%)	Depth(X)	COSMIC ID
1	DIS3	c.691C>T	p.His231Tyr	44	1,455	-
2	TRAF3	c.563C>T	p.Ala188Val	51	1,432	COSM6032802
3	TRAF3	c.769G>A	p.Val257Met	1.3	1,699	-

INTERPRETATION

The c.691C>T (p.His231Tyr) variant in the DIS3 gene has not been previously reported in cancer tissues including hematologic malignancies and its clinical significance is unclear due to unknown oncogenicity of the variant.

The c.563C>T (p.Ala188Val) variant in the TRAF3 gene has been previously reported in a cancer tissue but not in hematologic malignanies (N=1, COSM6032802) and the c.769G>A (p.Val257Met) variant in the TRAF3 gene has not been previously reported in cancer tissues including hematologic malignanies. The clinical significance of two variants is unclear due to unknown oncogenicity of the variants.

TEST INFORMATION

1.TEST METHOD

Target Region	24 genes
Tested Panel	Multiple Myeloma(MM) Panel
Target Enrichment Method	Hybridization with oligonucleotide probes (MM 1.0)
Massively Parallel Sequencing	MiSeqDX (150 bp x 2 paired-ends)
Bioinformatic Pipeline	BI_MM 1.0 (Alignment: BWA, Variant calling: VarScan2 & GATK)
Reference Genome	GRCh37/hg19

2.QC DATA

Sample(DNA) QC	Pass	Mean Coverage of Depth(X)	1415X
Library QC	Pass	% of Target Bases ≥ 50X	99.5%
Sequencing QC	Pass		

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3.TEST LIMITATIONS

- This test was performed using sequencing analysis, and can detect SNP and small-indel variants within the analyzed region, but not structural variations such as copy number variation (CNV) and gene rearrangement.
- The limit of detection for SNV and small-indel variants is approximately 5%.
- The detected variants in this test are not re-confirmed by Sanger sequencing, ddPCR or other confirmation methods.
- This test does not distinguish between germline and somatic variants. If the variant allele frequency of the mutation is close to 50% or 100%, the possibility of germline variant cannot be excluded.
- The variants detected in this test are classified into four (tier 1~4) according to the 2017 JMD guideline (J Mol Diagn 2017;19:313-327), and tier 4 variants are not reported.

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4. CLASSIFICATIONS

Somatic Variants are classified into four stages according to the evidence level and clinical significance of the mutation.
Tier 4 is not reported.

Tier1	Strong clinical significance	Level A or B evidence
Tier2	Potential clinical significance	Level C or D evidence
Tier3	Unknown clinical significance	Not observed at a significant allele frequency in the general or specific subpopulation databases, or no convincing published evidence of cancer association.
Tier4	Benign or likely benign	Observed at significant allele frequency in the general databases. No existing published evidence of cancer association.

EVIDENCE LEVEL

LevelA	Biomarkers related to predicting therapeutic response or resistance to FDA-approved therapies in specific cancer types or biomarkers included in professional guidelines as being related to therapeutic response or resistance to drugs, diagnosis or prognosis of cancer.
LevelB	A biomarker with a consensus among experts in a well-designed study that is associated with the treatment response or resistance to a drug, the diagnosis or prognosis in a specific cancer type.
LevelC	Predictive biomarkers of therapeutic response or resistance to FDA-approved drugs in other cancer types or biomarkers eligible for clinical trial participation, and biomarkers reported to be associated with cancer diagnosis or prognosis in several small studies.
LevelD	Biomarkers with preclinical trials or small studies or several case reports.

REFERENCES

- COSMIC(http://cancer.sanger.ac.uk)
- c-bioportal(http://www.cbioportal.org)
- Cancer Hotspots(http://cancerhotspots.org)
- OncoKB(http://oncokb.org)
- My Cancer Genome(https://www.mycancergenome.org/)
- The Clinical Knowledgebase(https://ckb.jax.org/)
- WHO classification of tumours of haematopoietic and lymphoid tissues(revised 4th edition)
- NCCN guidelines®

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5. GENE INFORMATION

ESSENTIAL GENE LIST

Gene	Target Exon No.	Reference Transcript	Gene	Target Exon No.	Reference Transcript	Gene	Target Exon No.	Reference Transcript
KRAS	All coding exons	NM_004985.4	NRAS	2-3	NM_002524.4	TP53	All coding exons	NM_000546.5

ADDITIONAL GENE LIST

Gene	Target Exon No.	Reference Transcript	Gene	Target Exon No.	Reference Transcript	Gene	Target Exon No.	Reference Transcript
ATM	All coding exons	NM_000051.3	ATR	All coding exons	NM_001184.3	BRAF	All coding exons	NM_004333.4
CCND1	1(Y44D, C47S), 5	NM_053056.2	CDK4	2(K22A, R24C)	NM_000075.3	CDK6	5(A197T)	NM_001145306.1
CRBN	All coding exons	NM_016302.3	CYLD	All coding exons	NM_001042355.1	DIS3	All coding exons	NM_014953.4
EGR1	All coding exons	NM_001964.2	TENT5C (FAM46C)	All coding exons	NM_017709.3	FGFR3	All coding exons	NM_000142.4
IDH2	4(R140Q, R172)	NM_002168.3	IRF4	3(K123R)	NM_002460.3	NR3C1	2(G369A)	NM_001024094.1
PSMB5	2	NM_002797.4	PTEN	All coding exons	NM_000314.6	RB1	All coding exons	NM_000321.2
TRAF3	All coding exons	NM_003300.3	XBP1	4(L167I)	NM_005080.3	ZFHX4	All coding exons	NM_024721.4

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