TEST REQUESTED: **Max Germline HRR Panel with BRCA1 & 2**

METHOD USED

Next Generation Sequencing

SAMPLE INFORMATION

Whole Blood

TARGETED GENES

ATM	*BARD1*	*BRCA1*	*BRAC2*	*BRIP1*	*CDK12*	*CHEK1*	*CHEK2*	*FANCL*	*PALB2*
PP2R2A	*RAD51B*	*RAD51C*	*RAD51D*	***RAD54L***					

Heterozygous Mutation Detected
NM_003579.4(RAD54L):c.1250C>T (p.Thr417Ile)
(Uncertain significance)

PRIMARY FINDINGS

Gene	CDS Variant	Amino Acid Change	Exon	Allele Frequency	Coverage	dbSNP ID	Pathogenicity (Clinvar/Varsome)
RAD54L	NM_003579.4:c.1250C>T	p.Thr417Ile	12	48%	2773	-	Uncertain Significance

INTERPRETATION SUMMARY

- This test identified a variant in ***RAD54L*** gene.

RECOMMENDATIONS

- Further investigations are recommended to check for repeat expansions and CNVs.
- Genetic counselling is recommended.

QUALITY THRESHOLD (Fractions of Targets with coverage above threshold, ≥100)					
100%	**90%**	**80%**	**70%**	**60%**	**50%**
99.64	100	100	100	100	100

INDIVIDUAL VARIANT INTERPRETATION

NM_003579.4(RAD54L):c.1250C>T (p.Thr417Ile)- Uncertain significance

A heterozygous missense variation in exon 12 of the RAD54L gene that results in the amino acid substitution of Isoleucine for Threonine at codon 417 (p.Thr417Ile) was detected. The p.Thr417Ile variant has not been reported in the 1000 genomes and gnomAD databases. The in silico predictions of the variant are possibly damaging by PolyPhen-2 (HumDiv) and damaging by SIFT, LRT, Mutation Taster2 tools.

Since supporting evidence is limited at this time, the clinical significance of this alteration remains unclear.

TEST METHODOLOGY

The 15 HRR genes (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PP2R2A, RAD51B, RAD51C, RAD51D, RAD54L*) sequencing was performed using next generation sequencing technology. DNA from the sample was subjected to library preparation. The enrichment of the coding regions for the genes of interest was performed with the use of target specific probes. The enriched libraries were sequenced to generate required sequence data.
The variants were called using in-house pipeline. In brief, the sequence data was processed to remove low quality bases, map to hg19 reference sequence, remove duplicate reads and call variants. The variants were prioritized and reported based on ACMG [1,2] guidelines.

LIMITATIONS

Inaccurate and/or incomplete clinical information might lead to misinterpretation of results. The analysis results are interpreted in the context of clinical observations, family history, and other lab reports provided. Only the variants located in genes that are potentially related to the proband's clinical phenotype are reported. Intronic variants, repeat expansions, copy number variations or chromosomal rearrangements may not be reliably detected with this test.

DISCLAIMERS

This report provides information about the patient's mutations that may aid the physician's decision making process, but this test should not be the sole source of information for making decisions on patient care and treatment. These tests should be interpreted in the context of standard clinical, laboratory, and pathological findings. Identification of a mutation in one or more of these genes does not guarantee activity of the drug in a given indication. Benign mutations and mutations in intronic regions have not been included in this report. Genetic counselling is recommended.

The information provided in this report was collected from various sources that we believe to be reliable and quality control procedures have been put in place to ensure the information provided is as accurate, comprehensive, and as current as possible. The information provided should only be utilized as a guide or aid and the decision to select any therapy option based on the information reported here resides solely with the discretion of the treating physician. Patient care and treatment decisions should only be made by the physician after taking into account all relevant information available including but not limited to the patient's condition, family history, findings upon examination, results of other diagnostic tests, and the current standards of care. This report should only be used as an aid and the physician should employ clinical judgment in arriving at any decision for patient care or treatment.

REFERENCES

1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine. 2015 May;17(5): 405-24.
2. David T. Miller et. al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine 2021; 23:1391–1398

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