Veritas
The Genome Company

myCancerRiskDNA Gene Panel Test

Name	Veritas myPC Demo	Sample Type	Saliva
DOB	May 05 1950	Sample Collected	Nov 12 2018
Sex	Female	Sample Received	Nov 19 2018
Provider	Veritas Doctor	Batch ID	mPC1234
Date of Report	Dec 14 2018	Customer ID	12345678

POSITIVE RESULT

BRCA1 c.5095C>T (p.Arg1699Trp), NM_007294.3, heterozygous, pathogenic variant

ADDITIONAL FINDINGS

No additional sequence or copy number variants of clinical significance were detected.

CLINICAL NOTE

Please note that this individual carries a well-established, pathogenic variant in *BRCA1*, which is known to cause Hereditary Breast and Ovarian Cancer syndrome (HBOC). This individual was reportedly diagnosed with ovarian cancer at the age of 45 years, which is consistent with the spectrum of cancer types and age of onset typically observed in individuals with HBOC. Given the reported family history of breast and prostate cancers on the paternal side of the family, it is possible that this individual inherited the variant from her father. Genetic testing of at-risk relatives for this *BRCA1* p.Arg1699Trp is strongly recommended. Additional information about HBOC can be found at GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1247/.

INTERPRETATION

Variant Information

***BRCA1* c.5095C>T (p.Arg1699Trp)** is a pathogenic variant that is associated with hereditary breast and ovarian cancer syndrome. It has been identified in >7 individuals with breast and/or ovarian cancer and has been shown to segregate with disease in multiple families (Rhiem 2007, Spurdle 2012, Laraqui 2013). Functional studies have demonstrated that the p.Arg1699Trp variant disrupts the function of the BRCA1 protein (Coquelle 2011, Bouwman 2013). This variant was detected in 2/22300 Finnish chromosomes by the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org; dbSNP rs55770810 referred to as p.Arg1720Trp using NM_007300.3). In ClinVar (ID:55396, accessed 9/16/18) this variant has been submitted as pathogenic by a ClinGen-approved expert panel (ENIGMA). In summary, the p.Arg1699Trp variant meets criteria (ACMG, Richards 2015) to be classified as pathogenic for hereditary breast and ovarian cancer syndrome.

REFERENCES

23289006, 17574969, 22889855, 21473589, 23867111

METHODS AND LIMITATIONS

Veritas' myCancer Risk test is a next-generation sequencing (NGS) assay for detecting variants in 40 genes. The test is performed on saliva or whole blood. Extracted genomic DNA is processed by a capture-based assay and sequenced on a next-generation sequencer (Illumina). For sample tracking and quality assurance, each sample is also assessed with the Infinium QC Array-24 microarray (Illumina). Sequencing is performed in Veritas Genetics' CLIA licensed and CAP accredited laboratory. Sequencing data are aligned to the hg19 (build 37.1) human reference genome. Data analysis is performed with Veritas Genetics' custom bioinformatics pipeline, which uses both Bayesian and Heuristic-based statistical variant callers.

Single nucleotide variants, small insertions/deletions, and copy number variants (selected genes) are detected. Promoter regions are included for a subset of genes *(APC 1A, APC 1B, BMPR1A, MLH1, MSH2,* and *PTEN)*. Copy number variants in selected genes are detected by analysis of NGS data. CNVs in *BRCA1, BRCA2, MLH1* and *MHS2* are detected at single-exon

METHODS AND LIMITATIONS

resolution. Copy number variants in *APC, ATM, CHEK2, GREM1, MSH6, PALB2, PMS2, PTEN, STK11*, and *TP53* are detected at multi-exon resolution (2 or more exons). *EPCAM* variant detection is limited to del/dup analysis of the 3' end of the gene, which is the only type of variant currently known to be disease-causing. For regions of high homology, del/dup analysis is not performed. Copy number variants are confirmed by MLPA. CNV detection is only performed for the specific genes listed above.

Only inherited (germline) variants are detected, and not somatic variants, mosaicism, or heteroplasmy. Inversions and complex structural rearrangements such as translocations are not detected. Positions with <10X coverage are excluded from reporting unless confirmed by an alternate technology.

Analytic sensitivity is 99.9%, 95% CI [99.79%, 100%] for SNVs and 93.6%, 95% CI [88.2%, 97.0%] for small insertions/deletions. Analytical positive predictive value is 99.1%, 95% CI [98.8%, 99.4%] for SNVs and 94.9%, 95% CI [89.8%, 97.9%] for small insertions/deletions.

Variants are classified as pathogenic, likely pathogenic, uncertain significance (VUS), likely benign, or benign based on the American College of Medical Genetics and Genomics (ACMG) guidelines (PMID: 25741868). Pathogenic, likely pathogenic variants, and VUSs are included in the report, whereas benign and likely benign variants are not reported. Intronic variants of uncertain significance are not reported beyond 2 base pairs from the coding region, but detected likely pathogenic or pathogenic variants up to 10 base pairs from the coding region are always reported. Pathogenic and likely pathogenic variants detected by NGS are confirmed with Sanger sequencing. Variants in high homology exons are confirmed with a long range PCR assay. VUSs are not confirmed with a secondary methodology. If a VUS is upgraded to a likely pathogenic or pathogenic classification in the future, then secondary testing would be recommended at that time for confirmation of the variant.

No clinical test is perfect. Current technology may not be able to detect some variants, and there may be other genes associated with inherited cancer syndromes that are not covered by this panel.

References

Zook JM. et al. Extensive sequencing of seven human genomes to characterize benchmark reference materials. Sci Data 2016;3:160025 doi: 10.1038/sdata.2016.25. PMID: 27271295

Mandelker D et al. Navigating highly homologous genes in a molecular diagnostic setting: a resource for clinical next-generation sequencing. Genet Med 2016;18:1282-1289. PMID: 27228465

Landrum MJ et al. ClinVar: public archive of interpretations of clinically relevant variants. Nuc Acids Res 2016;44(1):D862–D868. doi: 10.1093/nar/gkv1222. PMID 26582918

Richards 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. Genet Med 2015;17:405-424. PMID 25741868

Stenson PD et al. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet 2017;136:665-677. PMID: 28349240

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GENES TESTED

APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM (CNV only), FLCN, GREM1, HOXB13, MITF, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, POT1, PTCH1, PTEN, RAD51C, RAD51D, SMAD4, STK11, SUFU, TP53

AUTHORIZED SIGNATURES

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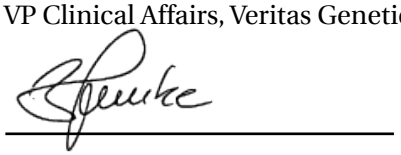

DISCLAIMER

This test was developed and its performance characteristics determined by Veritas Genetics. The analytical validation of this test meets CLIA and CAP requirements. The test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The Veritas Genetics laboratory is regulated under CLIA as qualified to perform high-complexity testing. If you have any questions about this report or wish to speak with one of Veritas Genetics' genetic counselors, please call 888-507-6619