Veritas a LetsGetChecked company | my CancerRisk

Name
Date of birth
Sex
Provider
Sample type

Sample ID
Sample collected
Sample received
Report date

POSITIVE RESULT

BRCA2 c.6591_6592delTG (p.Glu2198AsnfsTer4), NM_000059, heterozygous, pathogenic

ADDITIONAL FINDINGS

No additional variants of clinical significance were detected.

INTERPRETATION

BRCA2 NM_000059.3:c.6591_6592delTG (p.Glu2198AsnfsTer4), previously reported as 6819delTG, is a pathogenic variant associated with hereditary breast and ovarian cancer syndrome. This variant causes a frameshift at amino acid 2198 that results in premature termination 4 positions downstream. At this position, this is expected to result in absent protein (loss of function) which is an established mechanism of disease for BRCA2. This variant has been reported in multiple individuals with breast and/or ovarian cancer (Wooster 1995, White 2001, Edwards 2010, Zhang 2011, Zhang 2012, Finch 2015, Pritchard 2016, Pritzlaff 2017). This variant was detected in 1/246418 alleles by the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org; dbSNP rs80359605). In ClinVar (ID: 9319, accessed 3/11/20) this variant has been submitted as pathogenic by a ClinGen-approved expert panel (ENIGMA). In summary, the p.Glu2198AsnfsTer4 variant meets criteria (ACMG, Richards 2015) to be classified as pathogenic for hereditary breast and ovarian cancer syndrome. Biallelic pathogenic variants in BRCA2 have been associated with autosomal recessive Fanconi anemia. Although the disease association has been demonstrated, this variant has not been reported in individuals with autosomal recessive Fanconi anemia in the clinical literature.

You have a genetic variant that is known to be associated with an increased risk to develop Hereditary Breast and Ovarian Cancer Syndrome. This finding is considered significant by the ACMG because there are actions you can take to reduce your risk for serious disease.

Pathogenic and likely pathogenic variants in myCancerRisk genes are associated with increased cancer risks for both women and men. For some of the genes on this panel an exact cancer risk may not currently be known. Additionally, if a variant is detected in more than one gene, it may be difficult to assess the overall cancer risk. Medical management recommendations will depend on the gene in which the variant(s) was identified. Medical guidelines have not been established for all the genes included in this test. Therefore, the results may or may not have immediate health implications.

Genetic test results should be interpreted by a certified genetic counsellor or other qualified medical professional, in the context of the patient's clinical and family history, for accurate assessment of the personal risk. Any change in patient medical management or screening should only be considered after confirmation of the variant on a new sample with an alternative technology. For patients with a personal or family history of cancer, additional genetic testing may be indicated.

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METHODS AND LIMITATIONS

Veritas' myCancerRisk 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). Sequencing data is processed using bioinformatics pipeline with both Bayesian and Heuristic-based statistical variant callers and developed for this intended use. Mapping and analysis are based on the human genome build UCSC hg19 reference sequence.

Single nucleotide variants, small insertions/deletions, and copy number variants (in 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 (CNVs) are detected by a read-depth-based approach based on NGS data. CNVs in *BRCA1*, *BRCA2*, *MLH1* and *MHS2* are detected at single-exon resolution, CNVs 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. CNVs detection is only performed for the specific genes listed above and variants are confirmed by MLPA (Multiplex Ligation-dependent Probe Amplification).

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

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 beyond 2 base pairs from the coding region are not reported, 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 by Sanger sequencing when necessary. Variants in high homology exons are confirmed with a long-range PCR assay, except for exons 12-15 of the *PMS2* gene which are excluded from the analysis. VUSs are not confirmed with a secondary methodology. If VUS classification is upgraded to likely pathogenic or pathogenic in the future, then secondary testing would be recommended for confirmation of the variant at that time.

Analytic sensitivity is 99.9%, 95% CI [99.7%, 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.

NGS based tests 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

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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

VALIDATION

Technical Director: Medical Director: Approved by:

DISCLAIMER

Findings included in this report are based on current understanding and knowledge of genetic disease, variant classification may evolve over time as more information becomes available. For any clinical questions or to contact our genetic counselors, please contact us by email at genetic.counseling@veritasint.com or visit https://www.veritasint.com/en/contact for local contact details.

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