Jane Doe
Biological Sex: Female
Date of Birth: 11/13/2001
Sample ID: SM12805
Sample Type: BLOOD
Collection Date: 11/13/2024
Received Date: 11/14/2024

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Requisition ID:
RQ12345

Report Number:
RP12345

Report Date:
12/05/2024

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A pathogenic variant was identified in the PALB2 gene.

GENE	RESULT	VARIANT	ZYGOSITY
PALB2	Pathogenic	NM_024675.3:c.2167_2168del	Heterozygous

CLINICAL INFORMATION

This testing found that you have a change in a gene called *PALB2*, which is known to increase the risk of developing certain cancers, primarily breast, ovarian, and pancreatic.

Women with a pathogenic variant in *PALB2* have a 33-58% chance of developing breast cancer (PMID 25099575, 31841383), a 5% chance of developing ovarian cancer and a 1-4% chance of developing pancreatic cancer by age 80. Men have a 2-5% chance of developing pancreatic cancer and a 1% chance of developing male breast cancer by age 80 (PMID 31841383).

Variants in the *PALB2* gene associated with cancer predisposition are inherited in an autosomal dominant manner. This means that there is an increased risk for relatives to also have this variant. *PALB2* is also associated with a rare autosomal recessive condition called Fanconi anemia. Individuals need to inherit two variants, one from each parent, to have Fanconi anemia. This result is consistent with being a carrier for Fanconi anemia.

NEXT STEPS

- This is a medically actionable result that should be discussed with your healthcare provider to learn more about potential next steps and management guidelines, which may include screening for breast cancer earlier and more often, risk-reducing surgery, or medication.
- Family members are also at increased risk of having this variant. It is recommended that you share these results with your family members. Genetic testing can help identify who is at increased risk and would benefit from increased screening and management.
- Genetic counseling is recommended to discuss the significance of these results.
- Further information and resources may be available at https://www.facingourrisk.org/

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GENES ANALYZED

ACTA2, ACTC1, ACVRL1, APC, APOB, ATM, ATP7B, BAG3, BMPR1A, BRCA1, BRCA2, BTD, CACNA1S, CALM1, CALM2, CALM3, CASQ2, CHEK2, COL3A1, DES, DSC2, DSG2, DSP, ENG, FBN1, FLNC, GAA, GLA, HFE, HNF1A, KCNH2, KCNQ1, LDLR, LDLRAP1, LMNA, MAX, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH11, MYH7, MYL2, MYL3, NF2, OTC, PALB2, PCSK9, PKP2, PMS2, PRKAG2, PTEN, RB1, RBM20, RET, RPE65, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM127, TMEM43, TNNC1, TNNI3, TNNT2, TP53, TPM1, TRDN, TSC1, TSC2, TTN, TTR, VHL, WT1. See limitations in subsequent page(s).

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CLINICAL SUMMARY

A pathogenic variant was identified in the *PALB2* gene.

Clinical Information

The *PALB2* gene encodes a protein that may function in tumor suppression. This protein binds to and colocalizes with the breast cancer 2 early onset protein (BRCA2) in nuclear foci and likely permits the stable intranuclear localization and accumulation of BRCA2. [Source: NCBI]

Inheritance Pattern

Autosomal Dominant

Variant Details

Variant	NM_024675.3:c.2167_2168del
Category	Pathogenic

Evidence

The identified heterozygous deletion (c.2167_2168delAT) lies in exon 5 of the *PALB2* gene and is predicted to cause a frameshift and consequent premature termination of the protein (p.Met723ValfsTer21). Loss of function variants are known to be pathogenic in *PALB2*. This variant has been previously reported in patients affected with breast cancer [PMID 25099575, 24556926, 32339256].

This variant has been reported in the dbSNP database (rs587776416) and in the Genome Aggregation Database (gnomAD) with an allele frequency of 0.005%. In the ClinVar database, the identified variant has been reported as 'pathogenic' (VCV000136132.51) with respect to multiple conditions including hereditary breast ovarian cancer syndrome, familial cancer of breast and hereditary cancer-predisposing syndrome.

References

- Antoniou et al. *Breast-cancer risk in families with mutations in PALB2.* N Engl J Med. 2014; 371(371):497-506. PMID: 25099575.
- Yang et al. *Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families.* J Clin Oncol. 2020; 38(38):674-685. PMID: 31841383.
- Catucci et al. *PALB2 sequencing in Italian familial breast cancer cases reveals a high-risk mutation recurrent in the province of Bergamo.* Genet Med. 2014; 16(16):688-94. PMID: 24556926.
- Zhou et al. *Spectrum of PALB2 germline mutations and characteristics of PALB2-related breast cancer: Screening of 16,501 unselected patients with breast cancer and 5890 controls by next-generation sequencing.* Cancer. 2020; 126(126):3202-3208. PMID: 32339256.

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ADDITIONAL INFORMATION

- https://actionability.clinicalgenome.org/ac/Adult/ui/stg2SummaryRpt?doc=AC108&version=28602

TEST METHODS

- Specimen receipt, accessioning, data analysis, and interpretation is performed by MyOme Inc., 1455 Adams Drive, Suite 1150, Menlo Park, CA 94025, CLIA# 05D2203070. Blended Genome-Exome Sequencing, excluding data analysis and interpretation, is performed by Broad Clinical Labs LLC, 27 Blue Sky Dr, Burlington, MA 01803, CLIA#22D2055652.
- Genomic DNA obtained from the submitted sample was used to construct a PCR-free whole genome library and an exome library and sequenced using Illumina technology generating low-coverage whole-genome and higher coverage exome data. Reads were aligned to the NCBI GRCh38 reference assembly.
- Variants are interpreted and reported based on the standards and guidelines set forth by the American College of Medical Genetics and Genomics (ACMG). Classification categories include pathogenic (P), likely pathogenic (LP), variants of unknown significance (VUS), likely benign (LB) and benign (B). Reported variants only include those which are classified as P or LP. Variants in genes associated with phenotypes inherited in an autosomal recessive fashion need 2 P and/or LP variants to meet the threshold for reporting.
- All reported variants are confirmed by a secondary technology: SNVs are confirmed using Sanger sequencing.

TEST LIMITATIONS

- This test is designed to detect clinically relevant single-nucleotide variants and small insertions and deletions in the genes listed above. Currently variants cannot be reliably called in certain regions and are not analyzed: PMS2 exons 11-15, BMPR1A exons 12 and 13, TTN exons 173-197, and PTEN exon 9, RYR1 exon 91 and TGFBR1 exon 1. Additionally, sensitivity is reduced in TTN exons 147, 218 and KCNH2 exon 1. For HFE, analysis and reporting is limited to p.C282Y homozygotes and p.C282Y/H63D compound heterozygotes.
- This test does not detect variants in untranslated regions or more than 5bp into intronic regions.
- This test is not designed to detect aneuploidies or copy number variants.
- This test is not designed to detect certain types of variation including tandem repeat polymorphisms and low complexity repeats (including BRCA1/2 AluY insertion) and complex structural variants including inversions (including the Boland inversion), translocations, rearrangements, and gene fusions.
- Sensitivity to detect variants may be reduced in low complexity regions such as homopolymer regions (including MSH2 c.942+3A>T).
- There may be variants in this test that cannot be detected with the current technology. Only variants that are associated with conditions covered by this test are reported.
- A history of stem cell or bone marrow transplantation, or recent blood transfusion may impact the accuracy of the results.
- Like most tests, this test carries a risk of false negative or false positive results, which may be be caused by, without limitation, sample contamination from biological or non-biological sources, specimen marking issues, rare genetic variants interfering with analysis, and other technical issues and limitations.

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DISCLAIMERS

This test was developed, and its performance characteristics were determined, by MyOme, Inc., a clinical laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and College of American Pathologist (CAP) accredited to perform high complexity clinical laboratory testing. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). This test is a screening test for hereditary conditions resulting from pathogenic variants in 84 genes. This test provides no information for genomic variants in other genes. Like most tests, this test carries a risk of false negative or false positive results. Testing is unavailable for samples damaged by human error, lost/destroyed due to weather, transit issues or other problems beyond the control of MyOme. Test results should always be interpreted by a clinician in the context of clinical and familial data with the availability of genetic counseling when appropriate. MyOme is not responsible for the content of third-party websites referenced in this report.

REVIEWED BY

John Doe

John Doe, M.Sc.(Med)., Ph.D., FACMG

12/05/2024

Date

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