**Clinical Details:**

**FAMILIAL CANCER PANEL REPORT**

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| --- | --- |
| **Test Description:**  The BRCA1 & BRCA2 assay targets the familial cancer-related genes: *BRCA1, BRCA2.* | **RESULT SUMMARY:** |
|  |

**Test Result:**

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| --- | --- | --- | --- | --- | --- |
| Gene | EXON | REFERENCE | Nucleotide VARIANT | Protein Change | Classification |
| BRCA2 | ex11/27 | NM\_000059.3 | c.3326C>T | NP\_000050.2:p.(Ala1109Val) |  |

**Clinical Interpretation**

***BRCA2*:** BRCA2 encodes Breast And Ovarian Cancer Susceptibility Protein 2. Inherited mutations in BRCA2 (or the related BRCA1) confer increased lifetime risk of developing breast or ovarian cancer. Both BRCA1 and BRCA2 are involved in maintenance of genome stability, specifically the homologous recombination pathway for double-strand DNA repair.

The heterozygous variant c.[3326C>T];[=]: p.Ala1109Val was identified in exon 11 of the BRCA2 gene. This variant has been reported three times on the Breast Information Core (BIC) database as of unknown clinical significance and on ClinVar three times as an unclassified variant and twice as likely benign. Functional studies by Brough et al, The EMBO Journal 2012 31, 11601176 report that this variant disrupts the binding of BRCA2 and APRIN. APRIN is involved in the normal response to DNA damage, nuclear localisation of BRCA2 & RAD51 and efficient homologous recombination.This study found that this disruption reduced homologous recombination efficiency to 60% of wild type. However, the clinical implication of this disruption is unclear. Protein function prediction programs are inconsistent regarding the effect this variant may have on protein structure and function. This variant is present in population frequency data (ESP & ExAC) at frequencies less than 0.02% indicating it is not a known benign variant in these populations. Based on current knowledge this is a (Class 3) unclassified variant.

**Comment:**

For counselling and the assessment of the risk to the patient and other at risk family members please contact the appropriate genetic service.

**Test Description:**

**DNA Sequencing Analysis:** Automated Next-Generation Sequencing of all coding exons and flanking intron junctions of the BRCA1 & BRCA2 genes. The variant detected using NGS was confirmed using sanger sequencing.

**MLPA:** Gene dosage was assessed using Multiplex Ligation-Dependent Probe Amplification (MLPA) technology and kits available from MRC-Holland. The specific kits used are BRCA1 (P002D) & BRCA2 (P045C). This analysis detects large rearrangements.

Variants are described according to HGVS nomenclature version 19.01 (<http://varnomen.hgvs.org/>) with minor differences in accordance with Molecular Pathology policy. The policy as it pertains to this report is available by contacting the laboratory. Class 1 and 2 variants (benign and likely benign) are not reported.

**Confirmatory testing on a second independent sample is recommended. (IS THIS RELEVANT? DELETE FOR UV's)**

***Reference Sequence GenBank Accession Number:*** *BRCA1 NM\_007294.3; BRCA2 NM\_000059.3*

The nomenclature used throughout this report is in accordance with the Human Genome Variation Society (HGVS) guidelines, which can be found at www.hgvs.org/.

***This analysis does not exclude the possibility of other mutations not amenable to our analytical methods being present.***

**Disclaimer:**

*This laboratory assumes sample identification, family relationships, and clinical diagnoses are as stated on the request. Our clinical recommendations may be based on evidence from third-party data sources and should be interpreted in the context of all other clinical and laboratory information for this patient.*

Please contact the laboratory on 03 8559 8403 or 03 8559 5405 if you wish to discuss this report further.

**Reported by: Lumin Xue 13-May-2019 3:08 PM**

**Reported by: Jennifer Nakos 20-May-2019 9:51 AM**

**Authorised by:**