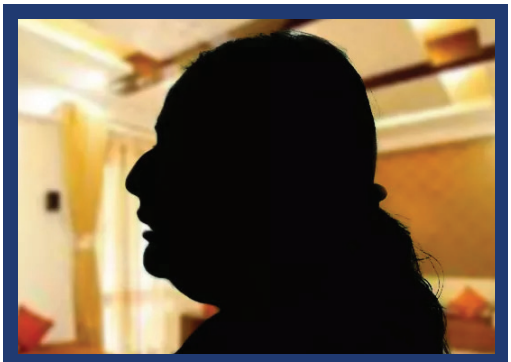
Classification of a *BRCA1* VUS mutation as potentially damaging - A pathway for therapeutic option enabled for patient



Gender: Female

Age: 57 years

Diagnosis: Ovarian cancer

Strand Test: Strand Germline Cancer Test

Conclusion: *BRCA1* VUS identified.

The VUS was classified as 'likely-damaging' based on similarity with a known mutation.

Patient may benefit from PARP inhibitor therapy based on her disease status and oncologists opinion.

Introduction

Humaira* was diagnosed with ovarian cancer at the age of 55 years and referred to Strand 2 years later. After diagnosis, she was prescribed chemotherapy as well as advised to undergo genetic counseling to understand whether her cancer was inherited or sporadic.

Patient Pedigree

Humaira's mother had been diagnosed with ovarian cancer and died at 78 years. Additionally, two of her mother's cousin sisters (second-degree relatives of Humaira) had also been diagnosed with breast cancer, both of them at the age of 35 years. One aunt had succumbed to the disease whereas the other one was a cancer survivor.

Humaira's paternal uncle was also diagnosed with cancer (the family was unable to provide more information about the type of cancer, in this case).

Based on the family pedigree, the Strand Germline Cancer Test was advised to Humaira to understand the genetic cause of the hereditary breast and ovarian cancer prevalent in the family.

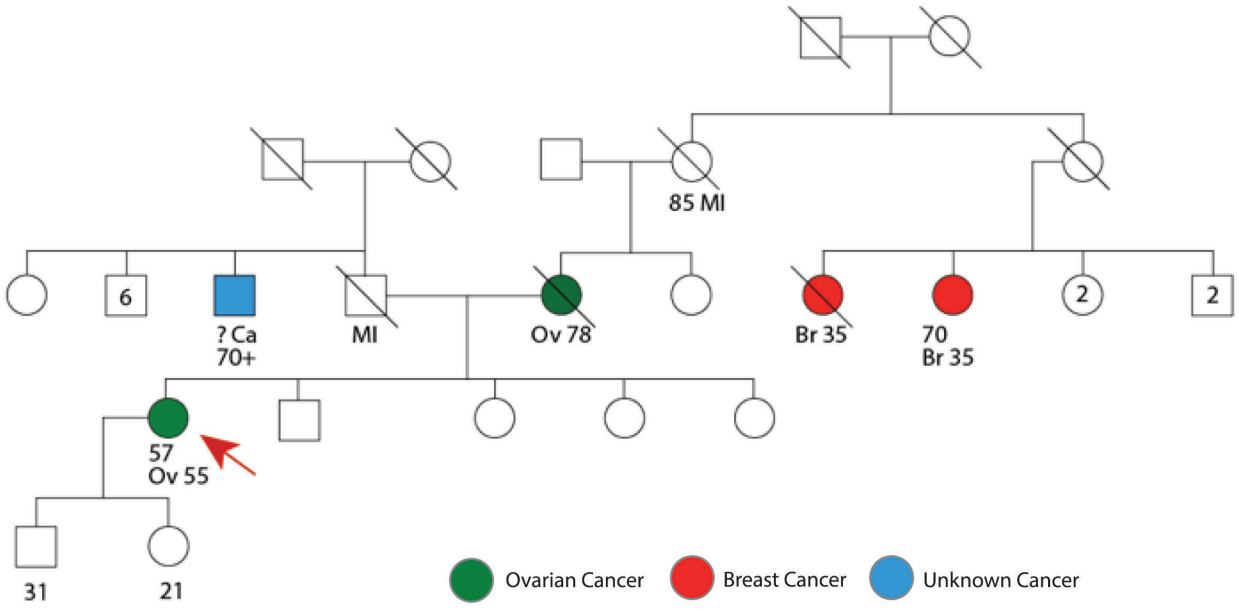


Figure 1. Family Tree of proband (indicated by the red arrow).

*Name changed to protect patient privacy

Results of the Genetic Test

Humaira was found to be heterozygous for a variant of the *BRCA1* gene. The mutation, in exon 17, was identified as a "variant of unknown significance with probable damaging effect' (VUSD) mutation.

RESULT VUSD

A heterozygous 'variant of unknown significance with probable damaging effect' (VUSD) was detected in exon 17 of the *BRCA1* gene.

Key Findings

Gene	Variation	Zygosity	Clinical significance
BRCA1	chr17:41215920G>C c.5123C>G p.Ala1708Gly	Heterozygous	Variant of Unknown Significance

Interpretation

A diagnosis of a VUS mutation is always problematic from a clinical viewpoint since there is inadequate literature support to help the patient with therapy or understanding their risk for further cancers.

At Strand Life Sciences, we use an extensive array of *in silico* analytical tools to determine the pathogenicity of the identified gene variants. *In silico* missense prediction tools (SIFT, LRT, Mutation Taster, PolyPhen-2, Mutation Assessor, FATHMM and Align-GVGD) suggest that this variant is probably damaging to the protein function. In this case, the missense substitution p.Ala1708Gly was found to be similar to another codon alteration (c.5123C > A, p.Ala1708Glu), that results in a similar substitution- p.Ala1708Glu. The latter substitution variant has been known to be pathogenic (Vaclová et al. 2016).

Additionally, the identified VUS alters a conserved residue in the BRCT domain of the *BRCA1* protein. This domain (residues 1650-1863) is involved in the interactions between *BRCA1* and other phosphoproteins.
Based on the similarity between the identified VUS and the previously known mutation, the VUS was classified as 'VUSD-Variant of Unknown Significance with a probable damaging effect'.

Conclusions

- Genetic testing as well as *in silico* analyses indicated that Humaira was heterozygous for a *BRCA1* VUS which is likely to be pathogenic.
- The classification of the patient's mutation from VUS to VUSD could make her eligible to receive PARP inhibitor therapy, based on her disease status, and per the recommendation of her oncologist. (Mirza et al. 2016; Oza et al. 2015; Swisher et al. 2017; Crafton et al. 2016; Jenner et al. 2016).
- Genetic testing for the identified *BRCA1* variant in other affected family members by Mutation Specific Test (Sanger) is recommended; to assess the co-segregation of this variation only with the affected family members, which may assist in determining the clinical significance of the variant.
- The physician can request reanalysis of the data and this is recommended on an annual basis. Data from this test is based on currently available scientific information.

References

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