IS DOUBLE HETEROZYGOSITY IN *BRCA* GENES INCOMPATIBLE WITH LIFE?

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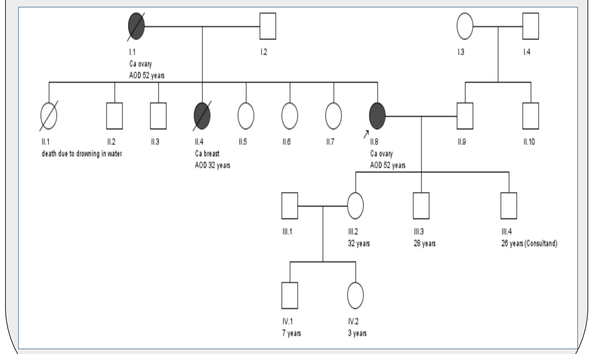
INTRODUCTION

- DH, also called trans-heterozygosity) is a rare finding where both *BRCA 1* and *BRCA 2* genes have heterozygous variations
- The estimated rate of DH is 0.22% to 0.83% in non-Ashkenazi Jewish women carrying BRCA mutations, while it can be as high as 1.8% in the Ashkenazi Jewish population.
- First case of a double heterozygous: Hungarian patient with breast and ovarian cancer reported in 1997

CASE DETAILS

PEDIGREE:



PATIENT PROFILE

- Proband (Female) aged 52 years , diagnosed with High grade serous ovarian cancer in Sept 2023 (AOD: 52 years)
- Symptoms: Abdominal distention and ascitic fluid accumulation
- Treatment: 3 cycles of NACT; surgery planned
- Other surgical history: Thyroidectomy done 20 years ago for benign gout
- Environmental / industrial exposure : None
- Menstrual history: Regular menstrual cycles; menopause attained nearly 8 to 9 years ago
- Prior genetic tests: None
- Family history: Proband's sister was diagnosed with breast cancer at 32 years and her mother was diagnosed with ovarian cancer at 52 years. They succumbed to their respective health conditions at 36 and 60 years, respectively.
- Consanguinity: None

RESULTS

Hereditary BRCA1/BRCA2 Test reported Two heterozygous '**pathogenic**' variants exon 10 of the *BRCA1* gene and another variant was detected in the essential splice donor site, in intron 2 of the *BRCA2* gene.

Key Findings

Gene	Variation	Zygosity	Inheritance	Variant classification
BRCA1	chr17:41245335dupA c.2214dupT p.Lys739Ter	Heterozygous	Dominant	Pathogenic
BRCA2	chr13:32890665G>T c.67+1G>T	Heterozygous	Dominant	Pathogenic

Disclaimer:

- *Quality: The average coverage was >300X for these regions with a read quality >Q30.*
- *For the deletion/duplication nomenclature, the most 3' position possible in the sequence is arbitrarily assigned to have been changed (Human Genome Variation Society guidelines).*

- The *BRCA1* variant causes a frameshift and an immediate premature termination of the protein. The resultant protein is likely to lack the major functional domains of the protein resulting in loss-of-function.
- The variant in intron 2 of the *BRCA2* gene as per in silico splice prediction tools (ASSP, MaxEntScan and NNSPLICE) predict that the variant is likely to impede splicing at the junction of exon 2 and intron 2 of *BRCA2* gene.

GENETIC COUNSELING

- The clinician expressed doubts about the compatibility of these mutations with life, prompting a post-test genetic counseling session.
- The genetic counseling session addressed these concerns explaining:
- The concept of double heterozygosity
- Its prevalence, and
- The need for appropriate surveillance.
- Further cascade testing for the proband's first degree relatives to determine if they harbor the same *BRCA* variants.

TAKE-AWAY FROM THE CASE

- The importance of both pre and post-test genetic counseling.
- Prevalence of DH in *BRCA* genes in non-Ashkenazi populations.
- Genetic testing to extend beyond identifying single-gene variants to include thorough analysis of multiple susceptibility genes.