CASE STUDY

Paternal Inheritance of a *BRCA* Mutation Leading to Breast Cancer

Gender: Female

Age: 53 years

Location: Hyderabad

Diagnosis: Breast Cancer

Strand Test: Germline Cancer Test

Conclusion:

- *Ad hoc* genetic testing advised
- Paternal inheritance of a *BRCA2* mutation confirmed by mutation specific testing
- Eligibility for PARP inhibitor therapy established

Quick Summary

- Chandana*, a 53-year old woman was diagnosed with breast cancer.
- Pedigree analysis showed that Chandana's father and paternal aunt had suffered from prostate and intestinal cancer, respectively. Inheritance of a pathogenic mutation was suspected.
- Strand Germline cancer test was advised to Chandana based on this pedigree analysis.
- A germline, pathogenic mutation in the *BRCA2* gene was identified in Chandana's genome, illustrating paternal inheritance of a *BRCA2* mutation.

Introduction

Breast cancer is predominantly a women's ailment, despite the fact that cases of male breast cancer have been documented. A quick look at some estimates shows that in 2021, 49,848 women and 1,115 men are expected to be lost to breast cancer (D'souza et al., 2013). It is not surprising, therefore, that when breast cancer cases are considered, an evaluation of the prevalence of breast and ovarian cancer among female relatives of the patient is given a lot of importance. One is more likely to remember maternal relatives who have had breast and / or ovarian cancer. However, you can inherit pathogenic mutations from your father's side as well. A case referred to Strand Life Sciences for genetic analysis, however, illustrates that paternal inheritance of germline mutations is equally evident and has to be considered.

Patient Profile

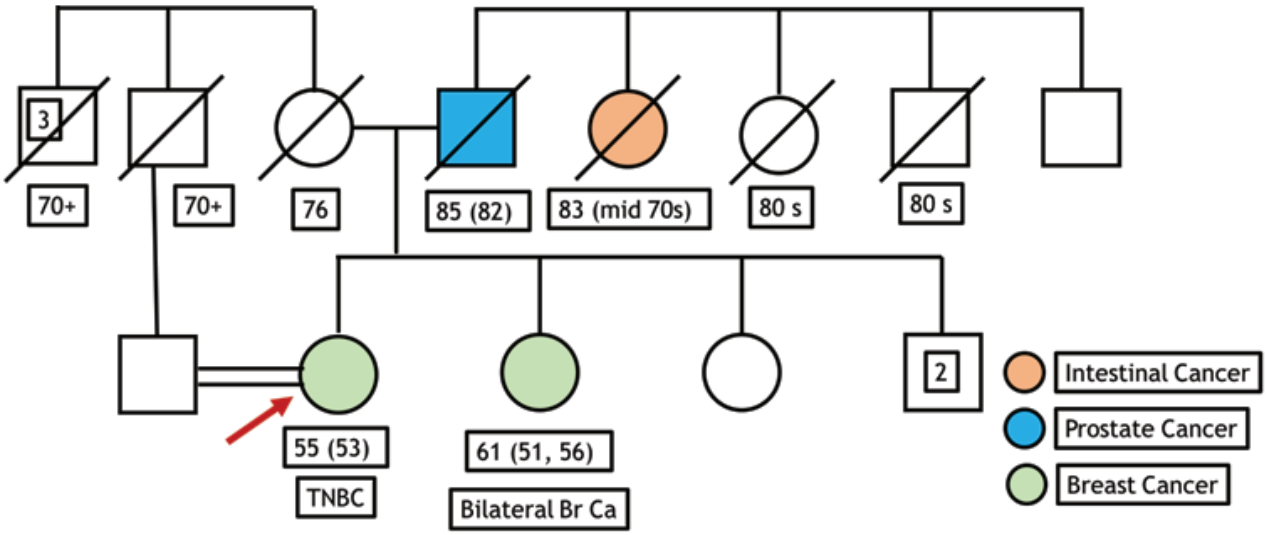
Chandana Pillarishetty had been experiencing breast pain for a few months. Three years ago, when she turned 50, she faced some minor health issues, but ignored it thinking it may be due to advancing age. The breast pain was, however becoming unbearable. Her elder sister had been diagnosed with bilateral breast cancer and was undergoing therapy for the same. Chandana wondered if she also had breast cancer, and the persistent pain was a warning sign. She consulted Dr. Praveen Dadireddy at a prominent hospital in Hyderabad. Dr. Dadireddy suspected the incidence of breast cancer and advised a biopsy of the breast tissue for histopathological analysis.

He also advised her to undergo genetic counselling in order to understand whether her breast cancer was caused by inherited mutations. Indian as well as international guidelines for management of breast cancer include genetic testing for patients who are around 50 years of age and are diagnosed with breast / ovarian cancer. (http://www.icmr.nic.in/guide/cancer/Breast_Cancer.pdf, https://www.asco.org/practice-guidelines/cancer-care-initiatives/genetics-toolkit/genetic-testing). Histopathological analysis showed that Chandana was suffering from triple-negative (TNBC: ER-, PR-, HER2-) breast cancer.

** Name changed to protect patient privacy*

Family Tree - Pre-Genetic Testing

Chandana's sister had been diagnosed with bilateral breast cancer, first at the age of 51 years and later again when she was 56. Their father had been diagnosed with prostate cancer at the age of 82 years and was undergoing treatment for the same. Chandana's paternal aunt was diagnosed with intestinal cancer, though the exact site of the cancer was not known. The maternal side of Chandana's family did not have a history of cancer.



Based on the prevalence of cancers in the family, the Strand Germline Cancer Test was prescribed for Chandana.

Results of Genetic Testing

The Strand Germline Cancer Test is designed to test for mutations in 19 genes that are known to be involved in hereditary breast and ovarian cancer predisposition. In Chandana's case, germline testing indicated that she was 'heterozygous' for a pathogenic mutation in the *BRCA2* gene.

RESULT Positive for a heterozygous **'pathogenic'** variant, which was detected in exon 11 of the *BRCA2* gene.

Key Findings

Gene	Variation	Zygosity	Clinical significance
BRCA2	chr13:32913599G>T c:5107G>T p.Glu1703T er	Heterozygous	Pathogenic

Key Interpretations

- Mutations in *BRCA1* and *BRCA2* genes are known to increase the risk for developing breast cancer. Women with *BRCA2* mutations have a 40-70% lifetime risk for breast cancer as well as an 11-18% risk of suffering from ovarian cancer (Petrucelli et al. 1993).
- The *BRCA2* mutation seems to have been inherited from the paternal side of the family. Women are much more likely to be referred for genetic counseling if the family history of breast or ovarian cancer is on their mother's side rather than their father's. Hence, the lack of cancer in the maternal side of Chandana's family could have been misleading. A complete reckoning of family history, recorded by Strand's genetic counsellor, however, shows the prevalence of multiple cancers in the paternal side of the family.
- The identification of the *BRCA2* mutation confirms the diagnosis of hereditary breast cancer in her. Mutation-specific testing* for the same *BRCA2* variant in her father affected with prostate cancer, and Chandana's sister confirmed that Chandana and her sister had indeed inherited this variant from their father.
- *BRCA2* is inherited in a dominant autosomal manner, meaning that one mutant copy of the gene is enough to create deficits in DNA repair mechanisms. Hence, patients like Chandana, who have one copy of the mutant *BRCA2* gene have a high risk of suffering from breast, ovarian, pancreatic and skin cancers (Petrucelli et al. 1993; Cicenas et al. 2017).

Treatment Options

Chandana was prescribed chemotherapy for the treatment of her triple-negative breast cancer.

One of the targeted therapies developed for treatment of ovarian cancer patients who have mutations in *BRCA1* and *BRCA2* genes is a class of drugs that can stop the activity of an enzyme called poly-ADP-ribose polymerase, or PARP for short. PARP is an enzyme engaged in the repair of breaks in double stranded DNA. Therefore, inhibition of this enzyme can actually promote the action of chemotherapy drugs that induce damage by breaking DNA strands in actively growing cancer cells. Drugs called PARP inhibitors have been approved for use in ovarian cancer patients bearing *BRCA1* and *BRCA2* mutations (Jenner *et al. 2016*; Crafton *et al. 2016*; Swisher *et al. 2017*; Mirza *et al. 2016;* Oza *et al. 2015*). PARP inhibitors are also thought to be effective in prostate cancer cells where stimulation of androgen-receptor mediated signalling leads to reduced expression of *BRCA1* and *BRCA2* genes, thereby creating conditions that mimic the presence of *BRCA1* and *BRCA2* mutations (also termed as '*BRCA*ness' of tumor cells) (Li *et al. 2017*). There is some evidence for a combinatorial use of inhibitors of PI3K and PARP for the treatment of breast and ovarian cancer (Condorelli & André 2017). Evidence from pre-clinical trials and some phase II trials suggests that PARP inhibitors may be effective in treating breast cancer patients bearing germline *BRCA1* and *BRCA2* mutations, despite receiving prior chemotherapy as well (Robert *et al. 2017*).

Preliminary results from clinical trials of PARP inhibitors in breast cancer patients with *BRCA1* and *BRCA2* mutations have shown better progression-free survival than that seen with chemotherapy (Robson et al. 2017; Robson 2017a).

The clinical application of PARP inhibitors is yet to receive FDA approval. However, in Chandana's case, her eligibility to receive this targeted therapy (once approved), has been established by genetic testing.

Conclusions

- Genetic testing confirmed the presence of a *BRCA2* mutation in Chandana.
- Identification of a *BRCA2* germline mutation has established Chandana's eligibility for PARP inhibitor therapy, in addition to chemotherapy, once it receives FDA approval.
- Chandana's case is a classic example of paternal inheritance of germline *BRCA* mutations.
- Chandana's elder sister should have been considered as an index case for germline testing of the entire family. Prior identification of the germline mutation in the family could have led to increased surveillance and prevention of actual incidence of cancer in Chandana's case.

The parameter marked with an * are not accredited by NABL and CAP.

Strand Germline Cancer Test

The Strand® Germline Cancer Test is a Laboratory Developed Test (LDT) that was developed and its performance characteristics determined by Strand Center for Genomics and Personalized Medicine at Strand Life Sciences.
This test covers 19 genes:

ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53

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