CASE STUDY

Hereditary Colon Cancer: Ad Hoc Genetic Testing Might Have Led to Better Surveillance Against Cancer

Quick Summary

- Saraswathi Subramanian*, 65 years, was diagnosed with adenocarcinoma of the colon.
- A prevalence of colon as well as gynecological cancer and sarcoma was noted in the maternal side of her family, during a genetic counselling session.
- Strand Germline Cancer Test was prescribed to Saraswathi to ascertain if her colon cancer was hereditary.
- A pathogenic variant of the *MLH1* gene was detected in her genome.
- Saraswathi's daughter, diagnosed with the same disease at a very young age of 32 years, should have been considered as an index case. Advice about risk assessment and mutation-specific testing could have been extended to the entire family, earlier.

Introduction

You can inherit your mother's eyes, your father's facial features, and perhaps even your uncle's height. How about adding a bit of cancer to the mix? About 5-10% of all cancers are hereditary; notable amongst them are breast, colorectal, ovarian, bowel and pancreatic cancer. A recent case referred to Strand Life Sciences is, in fact, an illustration of just this fact.

Patient Profile

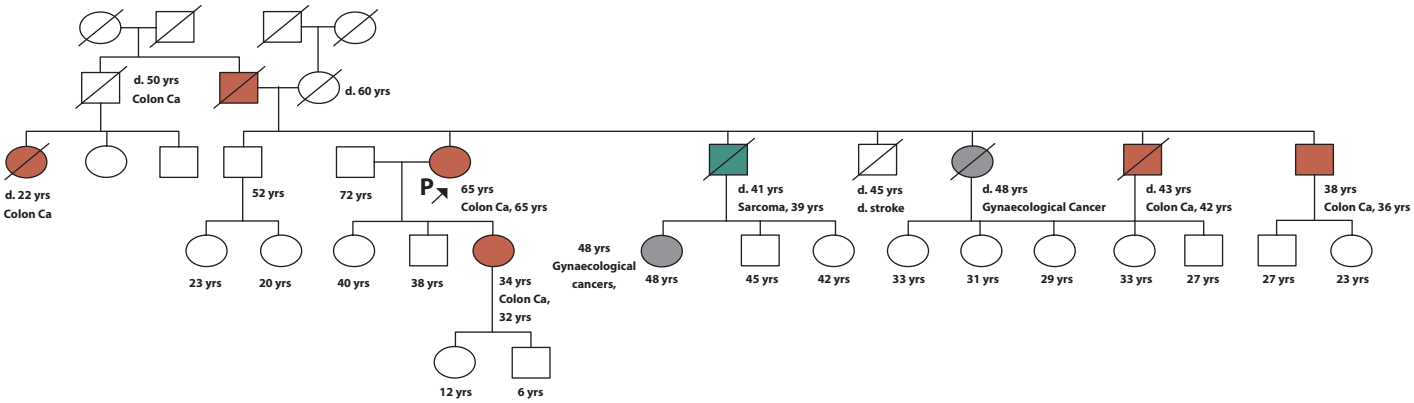
Celebrating her 65th birthday, Saraswathi Subramanian offered a silent prayer of thanks for a reasonably uneventful and smooth life so far. There had been a few tense years when one of her daughters had been diagnosed with colon cancer when she was just 32 years old. Cancer therapy had been successful and the disease was under control. Barring those 5 years, most of her life had been on a smooth course. She also reflected how her three brothers as well as her sister had been diagnosed with various cancers but she had been lucky to have escaped the same fate.

One brother had been diagnosed with sarcoma at the age of 39 years and had lost his life to cancer at the age of 41 years. His daughter (Saraswathi's niece), aged 48 years, had been diagnosed with a gynecological cancer, as well. Saraswathi's sister had passed away at the age of 48 years after suffering from a gynecological cancer. One of her younger brothers had been diagnosed with colon cancer at the age of 42 years and had succumbed to the disease after a year-long fight. Her youngest brother, aged 38 years was also battling colon cancer. Memories of how she had lost her father to colon cancer when he was 50 years old, also came flooding back.

Recently, she had noticed a change in her bowel movements, though. The frequency of bowel movements had increased. She also experienced pain in her lower abdomen occasionally. She consulted a leading oncologist at a large hospital in Bangalore for these health issues. The doctor understood her family history and noted the high prevalence of colon cancer in the paternal side. Medical investigations indicated a diagnosis of colon cancer, which was subsequently confirmed by imaging and histopathological findings. Saraswathi had colon adenocarcinoma, Grade1, T3N0Mx- Stage IIA.

Name changed to protect patient privacy

Family Tree Pre-Genetic Testing



Saraswathi's oncologist advised surgical excision of her colon cancer and also genetic testing to understand if this was an instance of hereditary colon cancer.

Results of Genetic Testing

The Strand Hereditary Colorectal Cancer Test was prescribed for Saraswathi. This test is designed to assess the presence of mutations in 19 genes associated with hereditary colorectal cancer predisposition and syndromes associated with it such as Lynch syndrome.

Key Findings

Gene	Variation	Zygosity	Inheritance	Clinical significance
MLH1	chr3:37092014G>A c.2141G>A p.Trp714Ter	Heterozygous	Dominant	Pathogenic

Saraswathi was found to be heterozygous for a pathogenic mutation in the *MLH1* gene.

Key Findings

- Saraswathi's colon cancer was caused by a pathogenic mutation in the *MLH1* gene.
- *MLH1* belongs to the mismatch repair family of genes and pathogenic mutations in these genes increases the risk for Lynch Syndrome.
- Considering strong family history of colon cancer on the maternal side, the diagnosis of colon cancer in Saraswathi's daughter should have been considered as an index case. If that had happened, MST could have been advised to the family earlier. Awareness about the prevalence of Lynch Syndrome in the family could have been achieved sooner.
- If ad hoc genetic testing had been advised and adopted, Saraswathi might have benefited from early periodic surveillance and dietary management strategies to minimize risk.
- Germline pathogenic variations in the *MLH1* gene in a heterozygous state are associated with Lynch Syndrome, which increases risk of colorectal (52%-82%), endometrial (25%-60%), gastric (6%-13%) and ovarian (4%-12%) cancers (Kohlmann & Gruber 1993).
- Lynch Syndrome, caused due to variations in the *MLH1* gene, is inherited in an autosomal dominant mode of inheritance, which means one copy of the altered gene in an individual is sufficient to increase the risk of developing cancer. Each first degree relative (children, siblings and parents) of the individual has a 50% chance of having this variation.

Conclusions

- The underlying cause of hereditary colon cancer in this family was identified as a pathogenic mutation in the *MLH1* gene.
- The proband and her family members were counselled about their risk for endometrial, gastric, and ovarian cancer.
- Mutation-specific testing* was advised to other family members as well.

Strand Germline Cancer Test

The Strand® Germline Colorectal 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 associated with high risk to colorectal cancer.

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

References

Kohlmann, W. & Gruber, S.B., 1993. Lynch Syndrome, Available at: http://www.ncbi.nlm.nih.gov/pubmed/20301390 [Accessed May 8, 2017].

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