CASE STUDY

Proactive Patient Paves the Way for Genetic Testing of Eight Family Members

Quick Summary

- Samar Mohite* was diagnosed with colon adenocarcinoma at the age of 49 years.
- Genetic counselling was advised to him in addition to surgical removal of his tumor.
- A pedigree analysis revealed the high incidence of colorectal as well as other cancers in his family.
- Genetic testing showed that Samar is heterozygous for a pathogenic mutation in the *MSH2* gene.
- Mutation-specific testing confirmed the presence of Lynch Syndrome in Samar's family.
- Proactive testing of Samar's children led to the identification of his son and three other cousins as carriers of the same pathogenic mutation. Mutation-specific testing also revealed that two other cousins and Samar's daughter have not inherited this pathogenic variant.
- Unaffected carriers in the family have been advised surveillance measures against cancers associated with Lynch Syndrome.
- *Ad hoc* genetic testing can add significant preventive, life-saving value in families with hereditary cancer syndromes.

Introduction

Genetic testing for assessment of personal risk of developing cancer is a relatively new concept in India. At Strand Life Sciences, we offer counselling for risk assessment and *ad hoc* genetic testing to determine risk for developing hereditary cancer. Our experience has been that people are interested, but they do take their time to come to a decision about getting themselves tested. Once in a while, though, we do see a refreshing change in this attitude when proactive people contact us and avail of our genetic counselling as well as testing services.

Patient Profile

Samar Mohite, age 49 years, had been experiencing episodes of constipation and diarrhea for a few weeks. He had experienced no trouble with his digestive system so far and hence these changes bothered him. He was especially alarmed when he passed fresh blood in his stool. This prompted him to seek medical advice. His general physician referred him to a leading oncologist in Pune. His oncologist suspected the presence of colorectal cancer. Hence, he advised Samar to undergo ultrasound and CT imaging to ascertain his hunch.

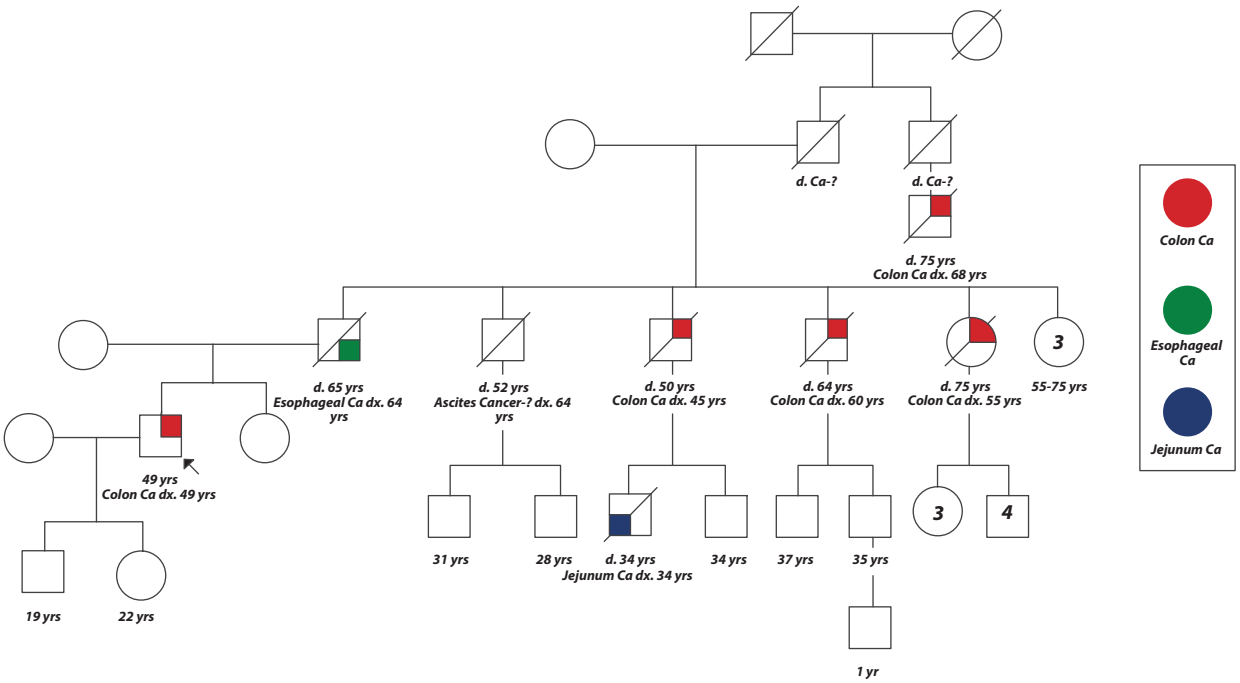
The ultrasonographic imaging revealed the presence of a 5.2 cms X 2.3 cms mass near the duodenal region. CT imaging showed eccentric thickening of the wall of the proximal transverse colon. The lumen of the colon was narrowed in an irregular fashion. Soft tissue stranding and multiple lymph nodes in the adjacent transverse mesocolon were also evident. Histological profiling of the tumor biopsy showed that Samar had an invasive poorly differentiated adenocarcinoma, grade pT2N0Mx and tumour infiltrating lymphocytes were present in the tumor biopsy.

Samar's oncologist advised him to undergo surgical removal of the tumor as well as genetic counselling to understand if there was a hereditary predisposition to the development of cancer at a young age. Samar Mohite underwent right hemicolectomy and excision of the diverticulum.

Name changed to protect patient privacy

Family Tree Pre- Genetic Testing

Samar and his wife Nikita* have two children, 19-year-old Rahul* and 22-year-old Sameeksha*. He was concerned about their well-being and hence he consulted Strand's genetic counsellor as soon as he was back on his feet, post-surgery.



At the genetic counselling session, Samar's extensive family history of cancer came to light:

- Samar's father had been diagnosed with esophageal cancer at the age of 64 years and succumbed to the disease one year later.
- Samar's father's younger brother had been diagnosed with colon cancer at the age of 45 years and lost his life to the disease when he was 50 years old. His son had been diagnosed with cancer of the jejunum at the age of 34 years and died from this cancer the same year.
- Two other paternal uncles had also died of cancer: One of them was diagnosed with colon cancer at the age of 60 years and succumbed to the disease at the age of 64 years. The other uncle's diagnosis at 51 years of age was unclear, but the presence of ascites fluid led to the conclusion that he was suffering from cancer and subsequently, died within a year due to the disease.
- Samar's paternal aunt had been diagnosed with colon cancer at the age of 55 years. She died at the age of 75 years, perhaps of unrelated causes.
- Samar's father has three more sisters, aged 55-75 years and they were free of cancer at the time of this pedigree analysis.
- Samar's father's cousin (uncle's son) had also been diagnosed with colon cancer at the age of 68 years and was lost to the disease at the age of 75 years.

This family history is strongly suggestive of the prevalence of Hereditary Non-Polyposis Colon Cancer (HNPCC), also known as Lynch Syndrome, in this family.

Analysis using the MMRPro software suggested a 94% chance of finding a mutation in a set of genes known as DNA mismatch repair (MMR) genes.

Samar agreed to undergo a germline cancer test to ascertain whether he indeed had a mutation in the MMR genes that led to the high incidence of cancer in his family.

Results of Genetic Testing

The Strand Germline Cancer Test, which covers 19 genes associated with hereditary colorectal cancer predisposition, was prescribed to Samar.

He was found to be heterozygous for a pathogenic variant in the *MSH2* gene.

RESULT **Positive** for a heterozygous **'pathogenic'** variant, which was detected in exon 4 of the *MSH2* gene.

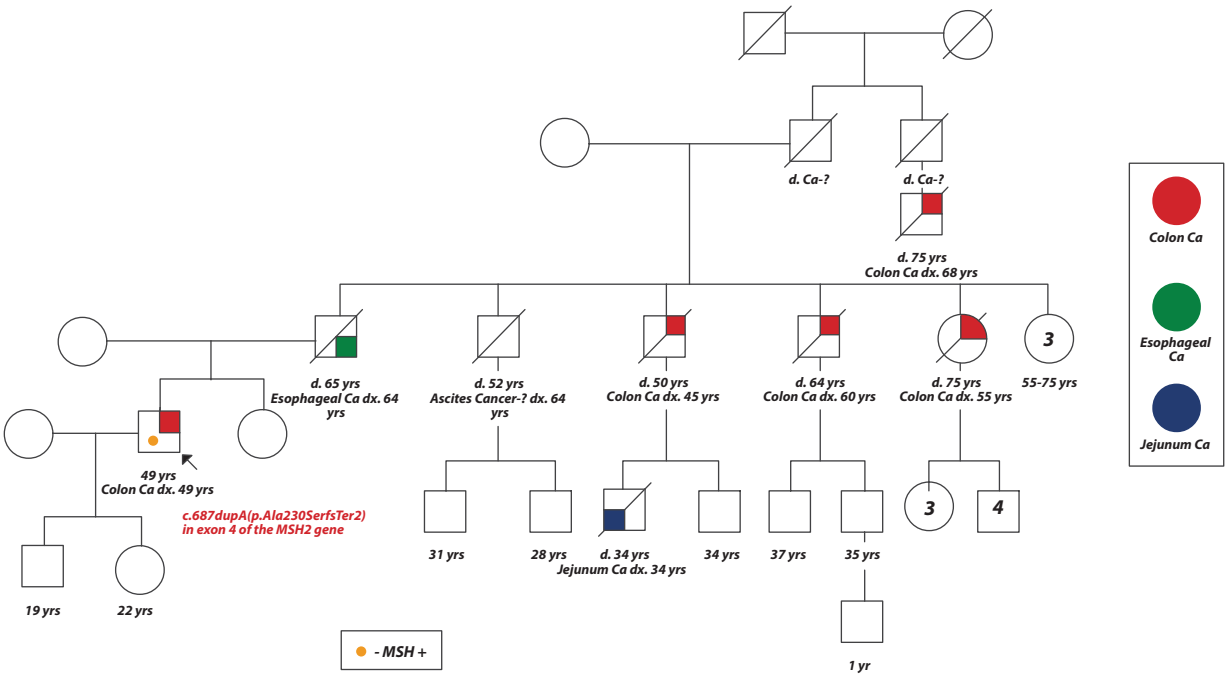
Key Findings

Gene	Variation	Zygosity	Clinical significance
MSH2	chr2:47639594dupA c. 687 dupA p.Ala230SerfsTer2	Heterozygous	Pathogenic

Key Interpretations

- Germline pathogenic variations in the *MSH2* gene are associated with Lynch Syndrome (Kohlmann & Gruber 1993).
- Although Samar is heterozygous (bearing only one copy of the mutant gene) the mutation is autosomal dominant. Therefore, only one copy of the mutant gene is sufficient to cause colorectal cancer in heterozygous individuals.
- People with Lynch Syndrome are at increased risk for developing other primary cancers like gastric, ovarian, small bowel, urothelial (ureter, renal pelvis), biliary tract, pancreatic, brain cancers (glioblastoma), sebaceous gland adenomas, and keratoacanthomas (Bhattacharya & McHugh 2017).

Family Tree Post-Genetic Testing



Samar was found to be a carrier for a pathogenic (disease-causing) variant in the *MSH2* gene. His immediate concern was to find out whether his children- Sameeksha and Rahul- were at risk or not.

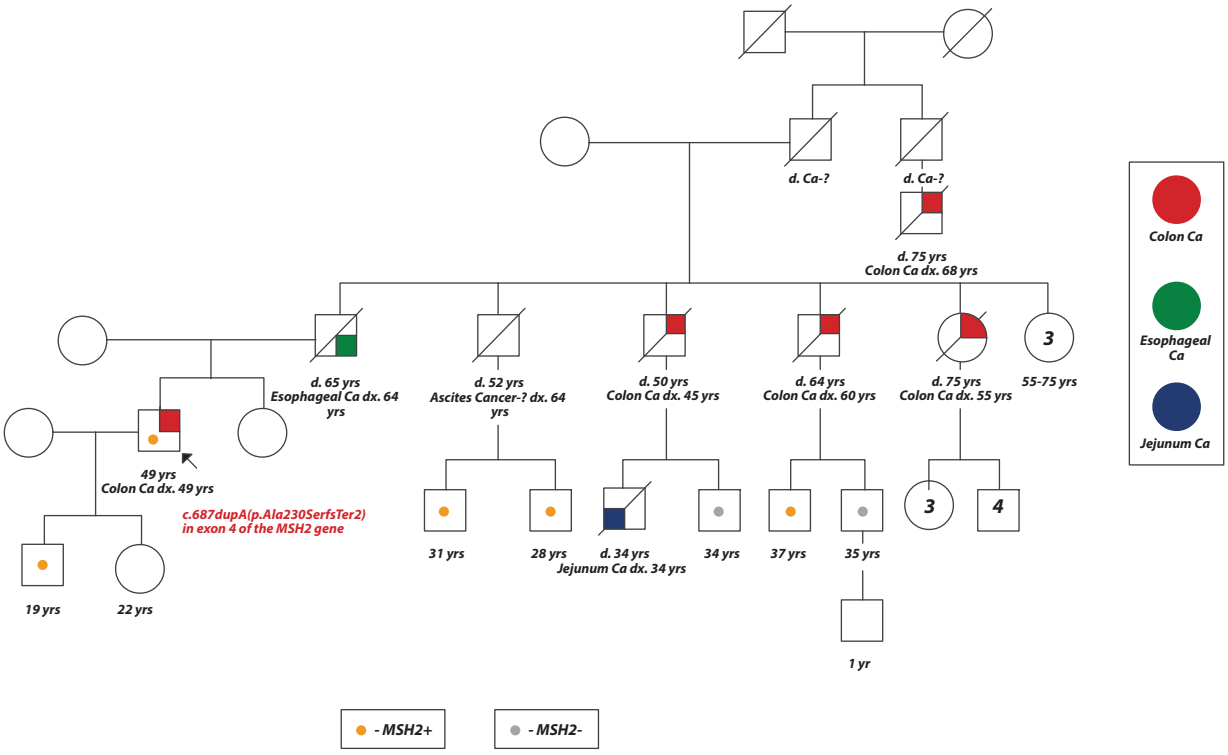
He also discussed his results with his cousins, progeny of the uncles and aunt who had died of various digestive system cancers. The entire family was alerted to the fact that they can indeed be at risk for development of colorectal as well as other cancers. Samar urged them to get tested as well, and not wait for the actual incidence of cancer to happen.

Mutation-Specific Testing

Once a heritable mutation is identified in an index patient, the presence or absence of the same gene mutation can be ascertained very quickly in other relatives. This genetic test is designed to identify only a particular gene variant and is, therefore, known as a Mutation-Specific Test (MST). MST offers a quick and efficient screening option for assessing the genetic status of the entire family, once the presence of a hereditary syndrome is ascertained by genetic testing as well as pedigree analysis.

Mutation-specific testing (MST) was advised to Samar's children as well as his cousins. All together, 7 family members agreed to take the test.

Results of MST



Mutation-specific testing revealed that Samar's son, Rahul, was heterozygous for the same *MSH2* variant, whereas his daughter, Sameeksha, was not. Likewise, two of Samar's cousins – aged 31 and 28 years - whose father had been diagnosed with cancer based on the presence of ascites fluid - are also heterozygous for the same mutation. Another cousin whose sibling had cancer of the jejunum was not a carrier for this mutation. Samar's cousins from another uncle – aged 37 and 35 years - were positive and negative for this mutation, respectively.

Conclusions

- Samar Mohite is heterozygous for a pathogenic mutation in the *MSH2* gene. This finding has led to the identification of Lynch Syndrome in his extended family.
- Mutation-specific testing was advised to Samar's children and also to his cousins, owing to his proactive interest in genetic testing.
- The carrier status of Samar's son and three of his cousins was confirmed to be positive through the results of the MST.
- Samar's daughter and two cousins were found to be negative for this mutation in the *MSH2* gene.
- Heterozygous individuals were advised about their risk for development of other primary cancers. These people can now adopt lifestyle changes and undergo periodic medical check-ups to catch cancer at the earlier stages, should they develop cancer later in life.

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 associated with hereditary colorectal cancer predisposition:

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

References

Bhattacharya, P. & McHugh, T., 2017. Lynch Syndrome, StatPearls Publishing. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28613748 [Accessed June 28, 2017].

Kohlmann, W. & Gruber, S.B., 1993. Lynch Syndrome, Available at: http://www.ncbi.nlm.nih.gov/pubmed/20301390 [Accessed June 26, 2017].

strand center
FOR GENOMICS & PERSONALIZED MEDICINE

Strand Center for Genomics & Personalized Medicine
(A unit of Strand Life Sciences Pvt. Ltd.)
UAS Alumni Association Building, Veterinary College Campus,
Bellary Road, Hebbal, Bangalore – 560 024
Phone: 1800-1022-695, support.strandx@strandls.com, www.strandls.com

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