strand center
FOR GENOMICS & PERSONALIZED MEDICINE

CASE STUDY

Identification of Li-Fraumeni Syndrome in a Family

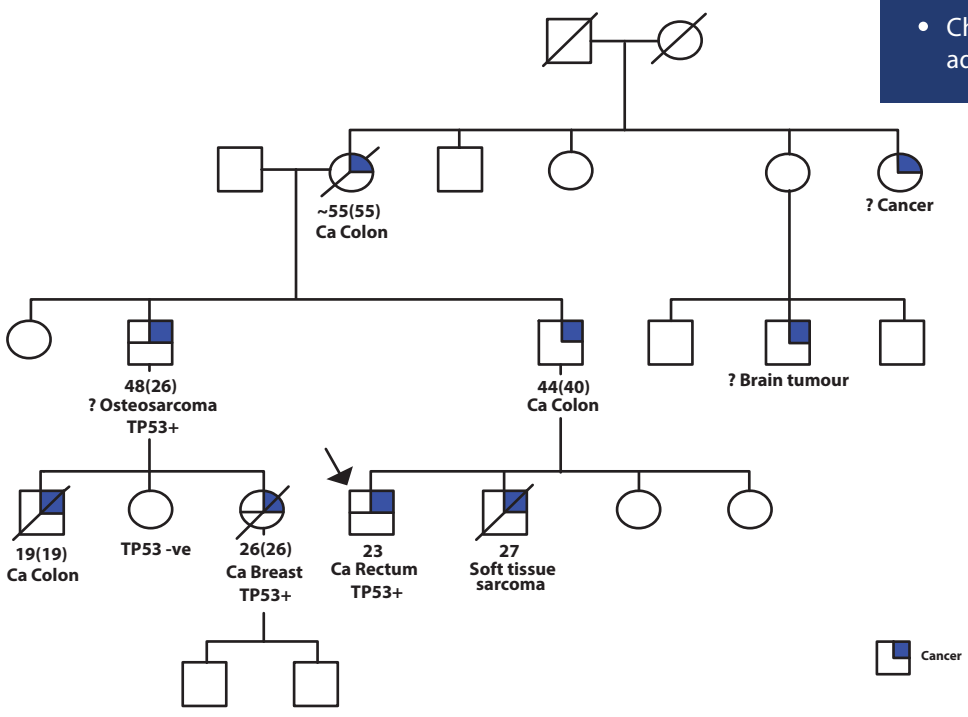
Patient Profile

A 23-year old man, Anmol Thakkar*, affected with rectal cancer was referred to a prominent cancer care centre in New Delhi. Anmol was a young man whose entire life turned upside down because of the recent revelation of cancer. The patient was further referred for genetic counselling for risk estimation of hereditary cancers.

Family History

His family has had an unusual chequered history of suffering from multiple cancers on his father's side. Anmol's brother had been diagnosed with soft tissue sarcoma at the age of 27 years and had succumbed to the disease. His father had been diagnosed with colon cancer at the age of 40 years. Anmol's paternal uncle had been diagnosed with osteosarcoma at the age of 48 years. Breast cancer was detected at the age of 26 years in Anmol's cousin sister. In a curious twist of fate, her brother (Anmol's cousin brother) also suffered from colon cancer, diagnosed at a tender age of 19 years and was lost to the disease. A third cousin sister was unaffected by cancer (pedigree shown below).

Family Tree- Pre-Test Genetic Counselling



Gender: Male

Age: 23 years

Location: Delhi

Diagnosis: Rectal cancer suggestive of Li Fraumeni's Syndrome

Strand Test: Strand Germline Cancer Test

Conclusion:

- Prevalence of Li-Fraumeni syndrome in family confirmed.
- Lifestyle management advice provided.
- Chemotherapy for rectal cancer advised.

*Name changed to protect patient privacy

Genetic Analysis

Based on the prevalence of personal and family history of early onset colon cancer, breast cancer, and osteosarcoma, Anmol was advised to take the Strand Germline Cancer Test. Genetic testing revealed that Anmol had a mutation in the *TP53* gene which might be the cause for his rectal cancer.

Genetic Testing

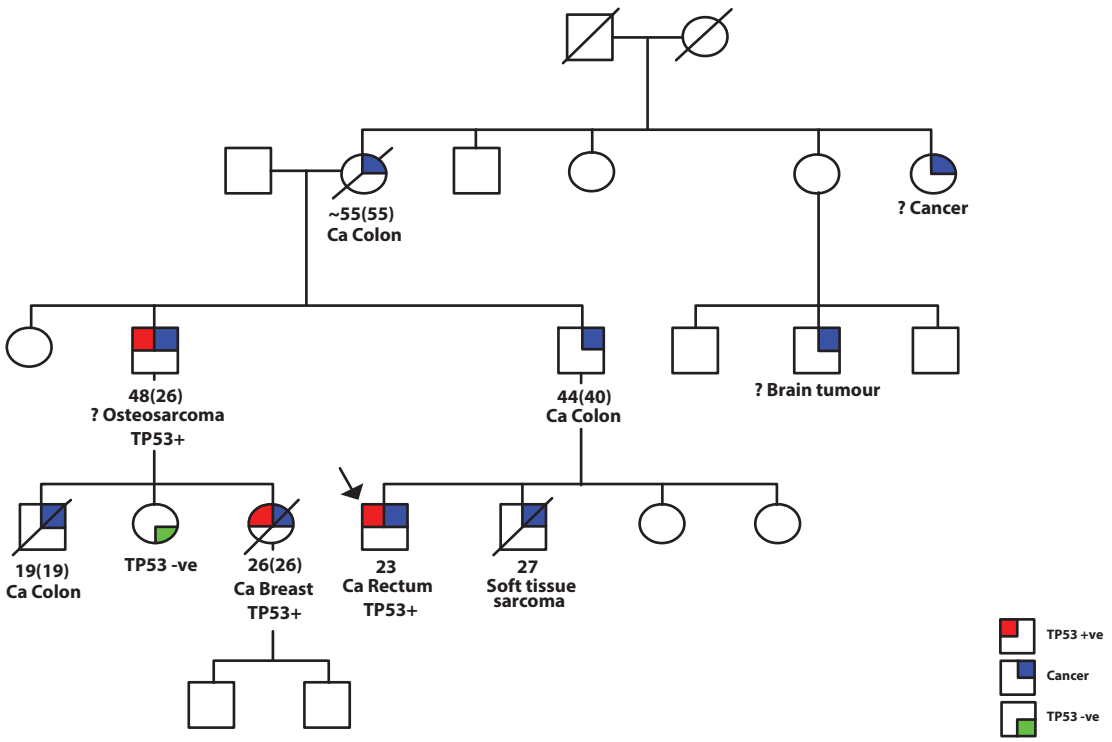
RESULT **VUSD** Upon genetic analysis, a heterozygous **'variant of unknown significance'** with probably damaging effect **(VUSD)** was detected in exon 7 of the *TP53* gene in Anmol's germline **DNA.**

Key Findings

Gene	Variation	Zygosity	Clinical significance
TP53	chr17:7577581A>G c.700T>C p.Tyr234His	Heterozygous	Variant of Unknown Significance

In order to further ascertain the significance of this variant, Anmol's family members were also advised to undergo mutation-specific testing. This is undertaken to understand the co-segregation of a VUS or VUSD mutation in the family. Essentially, if the clinical diagnosis of cancer amongst various family members correlates with their status as heterozygous carriers of the same mutation, then the VUS mutation is considered to exert damaging effects, possibly resulting in cancer.

Family Tree – Post-test Genetic Counselling



Key Interpretations

Mutations in the *TP53* gene result in the manifestation of Li-Fraumeni syndrome (LFS), which increases the risk of developing several types of cancer, particularly in children and young adults. The cancers most often associated with LFS include sarcoma, pre-menopausal breast cancer, brain tumors and adrenocortical carcinoma. There is no specific therapy available for *TP53* mutation carriers, however, people at risk are advised to manage their lifestyle to minimize their chances of developing cancers (Ross et al. 2017; Alderfer et al. 2017). Anmol was counselled accordingly.

Additionally, his first-degree and second-degree relatives were advised to undergo mutation specific testing. This testing revealed that Anmol's unaffected cousin sister did not have the *TP53* mutation that is present in three other affected family members.

This variant was previously detected in three family members affected with breast cancer, rectal cancer and osteosarcoma, respectively and was absent in two unaffected family members. Based on the guidelines for the interpretation of sequence variants from the American College of Medical Genetics and Genomics (ACMG) (Richards et al. 2015), this variant was re-classified as 'likely pathogenic' and now 'pathogenic' as it was found to be co-segregating with the disease in the family.

VUSD variant was reclassified as 'Pathogenic' based on the results of MST.

Conclusion

- Diagnosis of early onset rectal cancer in the proband and his family history of cancers in several first- and second-degree relatives such as osteosarcoma, breast cancer, colon cancer and soft tissue sarcoma was noted in this case. The incidence of various cancers within the family indicated a genetic predisposition suggesting inheritance of a germline mutation.
- The proband was advised genetic testing to determine the underlying cause of his own rectal cancer as well as multiple cancers within the family. The Strand Germline Cancer Test facilitated the identification of a *TP53* VUSD mutation (p.Tyr234His) in the patient's DNA.
- Co-segregation of this mutation with affected family members suggested that it is the disease causing mutation in the family. Identification of this *TP53* VUSD mutation and further co-segregation study established the fact that the family suffers from Li-Fraumeni syndrome, thereby explaining the high incidence of various cancers on the paternal side.
- Results of mutation-specific genetic tests in other family members in this case helped in estimation of risk for cancer of extended family members. The confirmation of their mutation status laid to rest the question as to what caused their early-stage cancers and allowed Anmol's surviving uncle to choose appropriate surveillance measures and manage his lifestyle to minimize risk.
- Mutation-specific testing showed that Anmol's cousin sister is not a carrier of the *TP53* mutation, reducing her risk for hereditary cancers. This has helped lower her anxiety to a great extent.

Strand Germline Test

The Strand Germline Cancer Test is designed to identify genes that are involved in several inherited cancers. The following genes are analyzed in samples from Li-Fraumeni cancer patients, as per international genetic testing guidelines. Genes assayed were:

APC, ATM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, EPCAM, KIT, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NBN, NF2, PALB2, PMS2, PTEN, RAD51C, RAD51D, RET, SDHB, SDHC, SDHD, SMAD4, TP53, TSC1, TSC2, VHL, WT1

References

Alderfer, M.A. et al., 2017. Should Genetic Testing be Offered for Children? The Perspectives of Adolescents and Emerging Adults in Families with Li-Fraumeni Syndrome. Journal of Genetic Counseling. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28303452 [Accessed May 3, 2017].

Richards, S. et al., 2015. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in medicine : official journal of the American College of Medical Genetics, 17(5), pp.405–24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25741868 [Accessed June 28, 2017].

Ross, J. et al., 2017. The psychosocial effects of the Li-Fraumeni Education and Early Detection (LEAD) program on individuals with Li-Fraumeni syndrome. Genetics in Medicine. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28301458 [Accessed May 3, 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

#StayAheadOfCancer

Strand Center for Genomics & Personalized Medicine is accredited by

CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS
8750941

Certificate No. M-0849

Strand Patient ID: GC134815062017