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Early-Onset Rectal Adenocarcinoma as the Initial Manifestation of Li-Fraumeni Syndrome Associated with a Germline TP53 p.R337H Variant: A Case Report and Literature Review

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Short Report

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Abstract

Background: Li-Fraumeni Syndrome (LFS) is a rare hereditary cancer predisposition disorder characterized by a wide spectrum of early-onset malignancies, particularly in children and young adults. While the most common neoplasms associated with LFS include soft tissue sarcomas, osteosarcomas, breast cancers, brain tumors, and adrenocortical carcinomas, growing evidence suggests an increased risk of colorectal cancer (CRC) in affected individuals. Herein, we report a case of rectal adenocarcinoma in a 34-year-old male with a confirmed germline TP53 variant.

Case presentation: The patient presented with a six-month history of hematochezia, tenesmus, increased bowel movements, and weight loss and was found to have anemia. Colonoscopy showed a friable, ulcerated rectal lesion, and biopsies confirmed poorly differentiated adenocarcinoma. Although treatment was initially declined, the patient returned five months later with disease progression and hepatic lesions suggestive of metastases. He underwent chemotherapy (CAPEOX regimen), external beam radiotherapy (EBRT), and abdominoperineal resection. Given his significant family history of cancer, including cerebral meningioma and leiomyosarcoma in his mother and gastric cancer in other relatives, genetic counselling and whole-exome sequencing (WES) were performed. A heterozygous germline TP53 p.R337H variant was identified and subsequently detected in his mother, sister, and niece through cascade testing, supporting a diagnosis of LFS.

Conclusion:

This case underscores the importance of considering LFS in young patients with colorectal cancer, particularly in the presence of a strong family history. Comprehensive genetic evaluation, including multigene panel testing or WES, should be considered for accurate diagnosis, risk stratification, and appropriate surveillance in affected families.

Introduction

Li-Fraumeni syndrome (LFS) is a rare inherited cancer predisposition disorder with an autosomal dominant pattern of inheritance. The syndrome is caused by germline mutations in TP53 tumor suppressor gene, resulting in markedly increased lifetime cancer risk. The estimated cumulative cancer risk approaches 70% in males and nearly 100% in females.

Although the classical tumor spectrum of LFS includes soft tissue sarcomas, osteosarcomas, premenopausal breast cancers, brain tumors, and adrenocortical carcinomas, recent studies have demonstrated that its tumor range is broader than previously recognized [1,2]. While colorectal adenocarcinomas account for a smaller fraction of LFS-associated malignancies, individuals with LFS have an approximately 2.8-fold higher relative risk of developing colorectal cancer (CRC) compared to the general population [3].

In an analysis of 397 patients among 64 families with classic LFS, CRC was diagnosed in 16 patients (4.0%) from 15 different families (23.4%), highlighting a potential predisposition to early-onset CRC in this population [4]. These findings suggest that LFS should be considered in the differential diagnosis of CRC in young adults, particularly those with significant family histories of cancer.

To further illustrate the clinical diversity of LFS and its association with gastrointestinal malignancies, we summarized 29 previously published case reports in Table 1 [5–28]. This table outlines key presenting symptoms, LFS diagnostic criteria, family history, clinical and laboratory findings, and genetic results, providing a comprehensive comparative overview of LFS cases. These reports were selected to highlight atypical or rare presentations, particularly gastrointestinal involvement, rather than to provide population-level risk estimates.

Table 1. Summary of 29 published case reports of Li-Fraumeni syndrome, including tumor types, genetic findings, age of onset, and whether colorectal cancer was the first manifestation.

The distribution of reported pathogenic TP53 variants across the gene is illustrated in Fig. 1.

Case presentation

A 34-year-old male presented to the internal medicine clinic with a six-month history of hematochezia, tenesmus, increased bowel movements, and unintentional weight loss. He had no significant past medical history and was not taking any medications. At initial consultation, he denied any known gastrointestinal malignancies among his first-degree relatives.

On physical examination, the patient appeared pale, with a body mass index (BMI) of 23 kg/m². No abdominal masses or hepatosplenomegaly were detected. Digital rectal examination revealed a firm, immobile mass approximately 5 cm from the anal verge. Laboratory evaluation revealed anemia (hemoglobin: 9.5 g/dL), while liver and renal function tests were within normal limits.

The patient was referred to the gastroenterology department. Colonoscopy revealed a 4 cm ulcerated, friable, infiltrative mass located 5 cm from the anal verge, causing partial luminal obstruction. No additional lesions were found throughout the colon. Multiple biopsies were obtained, and histopathological analysis confirmed poorly differentiated adenocarcinoma. According to the TNM staging system, the tumor was staged as T4N2M0. Immunohistochemical analysis demonstrated intact nuclear expression of MLH1, MSH2, MSH6, and PMS2, consistent with a mismatch repair-proficient (pMMR) phenotype, and the clinical profile fulfilled the Revised Bethesda and Chompret criteria, based on the presence of a rectal carcinoma before age 46 and multiple family members affected by malignancies, including soft tissue sarcomas and brain tumors (Tables 2 and 3).

Table 2. Diagnostic Criteria for Li-Fraumeni Syndrome

Criteria	Requirements
Classic LFS criteria	1. An individual diagnosed with a soft-tissue sarcoma before age 45 **AND** 2. A first-degree relative with any type of cancer before age 45 **AND** 3. Another first- or second-degree relative with any type of cancer before age 45 or a sarcoma at any age.
Birch Criteria	1. Two first- or second-degree relatives with LFS-related cancers, one diagnosed before age 45 **OR** 2. Three family members with any cancer, one diagnosed before age 45, and one diagnosed before age 40 **OR** 3. An individual with a tumor in the LFS spectrum (e.g., soft tissue sarcoma, osteosarcoma, breast cancer, brain tumor, adrenocortical carcinoma, leukemia, lung cancer) before age 36.
Chompret criteria	1. An individual with a tumor in the LFS spectrum before age 46, and at least one first- or second-degree relative with an LFS spectrum tumor (other than breast cancer if the individual has breast cancer) before age 56 or with multiple tumors **OR** 2. An individual with multiple tumors (excluding multiple breast tumors), two of which belong to the LFS spectrum, with the first occurring before age 46 **OR** An individual with adrenocortical carcinoma or choroid plexus tumor, regardless of family history.

Table 3. Clinical, Genetic, and Pathological Characteristics of a Young Male Patient with Rectal Adenocarcinoma and a Germline TP53 Variant

ID	sex	Age	Amsterdam	IHC-	Revised Bethesda	FRANKLIN	Location of cancer	TNM staging	stage	Pathology
L50	male	**34**	**POS**	**PMMR**	**POS** **Age≤50**	**TP53(p)** **APC(vus)** **MSH6(vus)** **PKHD1(LP)/** **FREM2(VUS)** **PAH(P)** **FREM2(VUS)** **LAMB2(VUS)**	RECTUM	**T4N2M0**	IV C	Poorly differentiated adenocarcinoma

Despite receiving a diagnosis of advanced rectal cancer, the patient initially declined further diagnostic workup and treatment. Five months later, he returned with worsened symptoms, including anal pain and mucus discharge. Repeat colonoscopy demonstrated a large polypoid mass 3–4 cm from the anal margin. CT imaging of the chest, abdomen, and pelvis was performed. Chest CT was unremarkable. Pelvic CT revealed bilateral pelvic lymphadenopathy and significant rectal wall thickening with luminal narrowing. Abdominal CT showed three hypodense hepatic lesions suggestive of metastases. Interestingly, serum carcinoembryonic antigen (CEA) was within normal limits.

Upon further evaluation, a detailed family history was obtained, revealing several malignancies in both first- and second-degree relatives: cerebral meningioma at age 49 and uterine leiomyosarcoma at 55 in his mother, gastric cancer at 60 in his great-aunt, gastric cancer at 35 in his great cousin, and small intestine sarcoma at 48 in his maternal grandmother (Figure 2). This pattern raised clinical suspicion of hereditary cancer syndrome.

Chemotherapy was initiated using the CAPEOX regimen (capecitabine and oxaliplatin), followed by external beam radiotherapy (EBRT) administered five to six times per week over a 6-week period. Due to progressive symptoms, including persistent rectorrhagia and anorectal pain, the patient underwent abdominoperineal resection (APR).

Despite aggressive treatment, the patient's condition continued to deteriorate due to widespread metastasis. He passed away nine months after the initial diagnosis from complications related to advanced cancer. This case underscores the aggressive nature of early-onset rectal adenocarcinoma in the context of Li-Fraumeni Syndrome (LFS) and highlights the critical importance of timely genetic assessment in young patients with suggestive family histories.

Microscopic analysis of the resected tumor revealed poorly differentiated adenocarcinoma with cribriform and glandular architecture, deep infiltration into the rectal wall, marked cytologic atypia, and a mitotic index of 12 per 10 high-power fields (Figure 3). IHC confirmed intact nuclear expression of MLH1, MSH2, MSH6, and PMS2. The retained expression of all four MMR proteins did not support an MMR-deficient phenotype (Figure 3C–F).

Given the early onset of colorectal cancer and a strong family history of LFS-spectrum tumors [29], the patient fulfilled the Chompret and revised Bethesda criteria (Tables 2 and 3). He was subsequently enrolled in the Iranian Hereditary Colorectal Cancer Registry [30] and referred for genetic counseling and

whole-exome sequencing. Genomic DNA extracted from peripheral blood leukocytes underwent whole-exome sequencing (WES) using the Agilent SureSelect v6 enrichment kit and Illumina HiSeq 4000 platform, achieving an average depth of 100X.

WES identified a heterozygous germline pathogenic TP53 variant, NM_000546:c.1010G>A, p.(Arg337His) (rs121912664), located in exon 10. This variant was confirmed by Sanger sequencing (Figure 4). Additional variants of uncertain significance (VUS) were noted in the MSH6 and APC genes (Table 4).

Table 4. Annotated whole-exome sequencing variants identified in the index patient .The table follows the nomenclature recommended by the Human Genome Variation Society (HKVC) where HGVS.c refers to the coding variant and HGVS.p to the protein level variant gnomAD genome aggregation database (provision of allele frequency), SIFT Sorting intolerant from tolerant, PolyPhen2 Polymorphism Phenotyping, version 2, CADD Combined annotation dependent depletion (provision of Phred score, version 1.6), DANN Deep neural network (provision of a functional prediction score), ClinVar Archive of interpretations of clinically relevant variants, ACMG American College of medical Genetics and genomics.

Gene.refGene	Zygosity		Exon number	HGVS.c	HGVS.p	Chr	avsnp150	InterVar_automated	ExAC_ALL
TP53	het	NM_000546.6	Exon 10	c.1010G>A	p.(Arg337His)	chr17	rs121912664	Pathogenic	8.52E-06
APC	het	NM_001127511	exon14	c.C7423A	p.L2475I	chr5	.	Uncertain significance	.
MSH6	het	NM_00128149:	exon2	c.A2377G	p.K793E	chr2	.	Uncertain significance	.
POLQ	het	NM_199420	exon29	c.C7640T	p.A2547V	chr3	rs2306211	Uncertain significance	0.0259
PKHD1	het	NM_138694	exon60	c.T10036C	p.C3346R	chr6	rs149798764	Uncertain significance	0.0003
PAH	het	NM_000277	exon8	c.G898T	p.A300S	chr12	rs5030853	Likely pathogenic	0.0004

Table 4 summarizes the annotated whole-exome sequencing results, including the pathogenic TP53 p.R337H variant and additional variants of uncertain significance in APC, MSH6, POLQ, and other cancer-related genes. Cascade genetic testing in the family revealed the same p.R337H variant in the patient's mother, sister, and her daughter (Figure 4). Unfortunately, despite aggressive multidisciplinary management, the patient died nine months after diagnosis due to widespread metastatic disease.

Discussion

Li-Fraumeni syndrome (LFS) is a rare hereditary cancer predisposition syndrome first characterized by Li and Fraumeni in 1969 following the observation of familial clustering of soft-tissue sarcomas [31]. It follows an autosomal dominant pattern of inheritance and is most commonly caused by germline pathogenic variants in the TP53 tumor suppressor gene, which plays a critical role in genomic stability through regulation of cell-cycle arrest, DNA repair, and apoptosis. The classical tumor spectrum in LFS includes soft-tissue and bone sarcomas, premenopausal breast cancer, central nervous system tumors, and adrenocortical carcinoma; however, more recent evidence indicates that the phenotypic range is broader and encompasses gastrointestinal malignancies, including colorectal cancer (CRC) [4, 7].

A 34-year-old man presented with early-onset rectal adenocarcinoma as the first and sole manifestation of LFS, a rare initial presentation of the syndrome. Although CRC is relatively uncommon in LFS, studies have reported a significantly higher risk compared with the general population, often occurring decades earlier [4, 33–36]. In the general population, the median age at CRC diagnosis is over 70 years, whereas in LFS, CRC may develop in the second or third decade of life [4, 34]. The rectal location in this case aligns with previous reports indicating a left-sided predominance of TP53-associated CRCs [37].

Genetic testing revealed a p.R337H missense variant in TP53, located in exon 10 and affecting the tetramerization domain of the p53 protein. Although this variant is well-characterized in Brazilian populations, with approximately 0.3% of individuals being carriers, it has not been previously reported in the Iranian population [39, 40]. Experimental evidence from murine models indicates that homozygous p.R337H carriers exhibit increased tumor susceptibility following carcinogen exposure, supporting its pathogenic potential [39]. Furthermore, Galante et al. demonstrated that the p.R337H variant exhibits reduced but sex-biased penetrance, with female carriers being more frequently affected by cancer [40].

Pedigree analysis of the patient revealed an autosomal dominant pattern of malignancies across three generations, fulfilling the clinical diagnostic criteria for LFS. The co-segregation of the p.R337H variant in his sister and other relatives further supports its role in this familial cancer cluster.

While brain tumors are well-recognized features of LFS, meningiomas are rarely reported within its tumor spectrum. Most central nervous system tumors in TP53 mutation carriers consist of choroid plexus carcinomas, gliomas, and medulloblastomas, often showing a bimodal age distribution [42, 43]. The presence of a meningioma in the patient's mother is therefore notable and may represent an expanded phenotypic expression associated with the p.R337H variant. This finding underscores the importance of considering broader CNS surveillance in affected families, even for tumor types that are uncommon in LFS. To contextualize our findings, we reviewed 29 previously published LFS case reports (Table 1). Only a small proportion involved colorectal cancer, and even fewer reported CRC as the initial or sole malignancy [44]. To our knowledge, this is the first reported case of early-onset rectal adenocarcinoma associated with a germline TP53 p.R337H variant in an Iranian patient. Notably, the patient also carried variants of uncertain significance in APC and MSH6; however, their clinical contribution to the phenotype remains unknown, and no causal inference can currently be made.

The reviewed cases consistently demonstrate the broad tumor spectrum and early-onset cancers characteristic of LFS, with breast cancer and sarcomas being the most frequent initial manifestations. Despite geographic and clinical heterogeneity, nearly all cases harbored pathogenic germline TP53 variants,

reinforcing the central role of p53 dysfunction in tumor predisposition. Only a minority of reports identified colorectal cancer as the first presenting malignancy, indicating that while possible, CRC remains an uncommon initial phenotype in LFS.

Our case highlights that early-onset CRC can serve as a sentinel manifestation of LFS and emphasizes the importance of routine germline testing for timely risk stratification and cascade screening in affected families. These findings support referral for comprehensive genomic testing including multigene panels or whole-exome sequencing in young CRC patients, particularly when family history is suggestive. The patient also carried variants of uncertain significance in APC and MSH6; however, their clinical contribution to the phenotype remains unknown, and no causal inference can currently be made.

Conclusion

This case emphasizes the importance of considering Li-Fraumeni syndrome in young colorectal cancer patients with a suggestive family history. The identification of the TP53 p.R337H variant in an Iranian patient adds to the reported geographic and phenotypic spectrum associated with this germline variant. Early-onset CRC as the initial manifestation of LFS is rare, highlighting the importance of considering comprehensive germline genetic evaluation in young patients, particularly when the family history is suggestive of a hereditary cancer predisposition syndrome.

Abbreviations

LFS - Li-Fraumeni Syndrome

TP53 - Tumor Protein p53

CRC - Colorectal Cancer

CEA - Carcinoembryonic Antigen

EBRT - External Beam Radiotherapy

APR - Abdominoperineal Resection

MMR - Mismatch Repair

IHC - Immunohistochemistry

FDR - First-Degree Relatives

HPFs - High-Power Fields

FAP - Familial Adenomatous Polyposis

LS - Lynch Syndrome

CT - Computed Tomography

CAPEOX - Capecitabine and Oxaliplatin (chemotherapy regimen)

PCR - Polymerase Chain Reaction

NGS - Next Generation Sequencing

HiSeq4000 - A specific model of Illumina sequencing platform

Declarations

Authors' contributions

LeG and LaG conceived and designed the study. LeG and A.T. contributed to data collection, genetic analysis, interpretation of the results, and preparation of the manuscript. A.M. contributed to pedigree construction and family history documentation. A.A. contributed to consultation and interpretation of the genetic and clinical findings. A.Af. performed and interpreted the pathological assessment. N.K. contributed to data analysis and manuscript preparation. H.V. and LaG critically reviewed and revised the manuscript. LeG, LaG, A.T., and N.K. wrote the main manuscript text. All authors reviewed and approved the final manuscript.

Statements and Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.REC.1396.164) and was conducted in accordance with the Declaration of Helsinki and its later amendments.

Consent to Participate

Informed consent was obtained from the participants included in the study.

Consent for Publication

Written informed consent for publication of the participant's clinical and genetic information was obtained from the participant.

Data Availability

The demographic, clinical, and molecular genetic data generated and/or analyzed during the current study are available from the corresponding author upon reasonable request, subject to applicable ethical and privacy restrictions.

References

1. Chompret A, Brugières L, Ronsin M, Gardes M, Dessarps-Freichey F, Abel A et al (2000) P53 germline mutations in childhood cancers and cancer risk for carrier individuals. Br J Cancer 82:1932–1937. https://doi.org/10.1054/bjoc.2000.1167
2. Guha T, Malkin D (2017) Inherited TP53 mutations and the Li-Fraumeni syndrome. Cold Spring Harb Perspect Med 7:a026187. https://doi.org/10.1101/cshperspect.a026187
3. Ruijs MWG, Verhoef S, Rookus MA, Pruntel R, van der Hout AH, Hogervorst FBL et al (2010) TP53 germline mutation testing in 180 families suspected of Li-Fraumeni syndrome: mutation detection rate and relative frequency of cancers in different familial phenotypes. J Med Genet 47:421–428. https://doi.org/10.1136/jmg.2009.073429
4. Wong P, Verselis SJ, Garber JE, Schneider K, DiGianni L, Stockwell DH et al (2006) Prevalence of early onset colorectal cancer in 397 patients with classic Li-Fraumeni syndrome. Gastroenterology 130:73–79. https://doi.org/10.1053/j.gastro.2005.10.014
5. Sekiguchi K, Motoo I, Ando T, Noguchi A, Fukuda R, Nomura K et al (2025) Early-onset colorectal cancer in a patient with Li-Fraumeni syndrome: a case series and literature review. Intern Med 64:3244–3251. https://doi.org/10.2169/internalmedicine.4945-24
6. Cirauqui B, Morán T, Estival A, Quiroga V, Etxaniz O, Balana C et al (2020) Breast cancer patient with Li-Fraumeni syndrome: a case report highlighting the importance of multidisciplinary management. Case Rep Oncol 13:130–138. https://doi.org/10.1159/000505684
7. Kast K, Krause M, Schuler M, Friedrich K, Thamm B, Bier A et al (2012) Late onset Li-Fraumeni syndrome with bilateral breast cancer and other malignancies: case report and review of the literature. BMC Cancer 12:217. https://doi.org/10.1186/1471-2407-12-217
8. Arango-Ibañez JP, Parra-Lara LG, Zambrano ÁR, Rodríguez-Rojas LX (2024) Li-Fraumeni syndrome presenting with de novo TP53 mutation, severe phenotype and advanced paternal age: a case report. Hered Cancer Clin Pract 22:1. https://doi.org/10.1186/s13053-023-00272-2
9. Nandikolla AG, Venugopal S, Anampa J (2017) Breast cancer in patients with Li-Fraumeni syndrome: a case-series study and review of literature. Breast Cancer (Dove Med Press) 9:207–215. https://doi.org/10.2147/BCTT.S134241
10. Klein JD, Kupferman ME (2017) Li-Fraumeni syndrome presenting as mucosal melanoma: case report and treatment considerations. Head Neck 39:E20–E22. https://doi.org/10.1002/hed.24594
11. Jhaveri AP, Bale A, Lovick N, Zuckerman K, Deshpande H, Rath K et al (2015) The benefit and burden of cancer screening in Li-Fraumeni syndrome: a case report. Yale J Biol Med 88:181–185
12. Watanabe H, Fujishima F, Motoi T, Aoyama Y, Niihori T, Takahashi M et al (2022) Comprehensive genomic profiling of a unique liposarcoma arising in a patient with Li-Fraumeni syndrome and the novel detection of c-myc amplification: a case report. Diagn Pathol 17:93. https://doi.org/10.1186/s13000-022-01264-x
13. Kai M, Kubo M, Shikada S, Hayashi S, Morisaki T, Yamada M et al (2022) A novel germline mutation of TP53 with breast cancer diagnosed as Li-Fraumeni syndrome. Surg Case Rep 8:197. https://doi.org/10.1186/s40792-022-01546-y
14. Edmondson S, von Itzstein MS, Reys B, Mayer M, Gagan J, Gerber DE (2022) Distinct NSCLC EGFR variants in a family with Li-Fraumeni syndrome: case report. JTO Clin Res Rep 3:100368. https://doi.org/10.1016/j.jtocrr.2022.100368
15. Li X, Kang J, Pan Q, Sikora-Wohlfeld W, Zhao D, Meng C et al (2016) Genetic analysis in a patient with nine primary malignant neoplasms: a rare case of Li-Fraumeni syndrome. Oncol Rep 35:1519–1528. https://doi.org/10.3892/or.2015.4501
16. Fang Z, Su Y, Sun H, Ge M, Qi Z, Hao C et al (2021) Case report: Li-Fraumeni syndrome with central nervous system tumors in two siblings. BMC Pediatr 21:588. https://doi.org/10.1186/s12887-021-03070-8
17. Puzik A, Uhl M, Ruf J, Schumacher T, Kontny U (2021) Unusual course of disease and genetic profile in Li-Fraumeni syndrome-associated osteosarcoma: a case report. Hered Cancer Clin Pract 19:44. https://doi.org/10.1186/s13053-021-00202-0
18. Barbosa OV, Reiriz AB, Boff RA, Oliveira WP, Rossi L (2015) Angiosarcoma in previously irradiated breast in patient with Li-Fraumeni syndrome: a case report. Sao Paulo Med J 133:151–153. https://doi.org/10.1590/1516-3180.2012.6740004
19. Aversa JG, De Abreu FB, Yano S, Xi L, Hadley DW, Manoli I et al (2020) The first pancreatic neuroendocrine tumor in Li-Fraumeni syndrome: a case report. BMC Cancer 20:256. https://doi.org/10.1186/s12885-020-06723-6
20. Poli T, Laganà F, Caradonna L, Gobbi R, Corradi D, Sesenna E (2005) Primary orbital liposarcoma in Li-Fraumeni cancer family syndrome: a case report. Tumori 91:96–100. https://doi.org/10.1177/030089160509100121

21. Ånensen N, Skavland J, Stapnes C, Ryningen A, Børresen-Dale AL, Gjertsen BT et al (2006) Acute myelogenous leukemia in a patient with Li-Fraumeni syndrome treated with valproic acid, theophyllamine and all-trans retinoic acid: a case report. Leukemia 20:734–736. https://doi.org/10.1038/sj.leu.2404117
22. Yang Y, Lee J, Woo CG, Lee OJ, Son SM (2024) Epithelioid angiomyolipoma of the liver in a patient with Li-Fraumeni syndrome: a case report. Diagn Pathol 19:16. https://doi.org/10.1186/s13000-023-01418-5
23. Wu X, Tian S, Liang B, Yang Q, Ng H, Wu S et al (2020) A young adult patient with Li-Fraumeni syndrome-associated glioblastoma: case discussion and literature review. Glioma 3:71–75. https://doi.org/10.4103/glioma.glioma_17_20
24. Marks JA, Liu SV (2023) NSCLC with synchronous EGFR mutations in Li Fraumeni syndrome: a case report. JTO Clin Res Rep 4:100521. https://doi.org/10.1016/j.jtocrr.2023.100521
25. Prejac J, Dedić Plavetić N, Gotovac Jerčić K, Borovečki F (2021) A first report of a rare TP53 variant associated with Li-Fraumeni syndrome manifesting as invasive breast cancer and malignant solitary fibrous tumor. World J Surg Oncol 19:254. https://doi.org/10.1186/s12957-021-02370-8
26. Ryckx S, De Schepper J, Giron P, Maes K, Vaeyens F, Wilgenhof K et al (2023) Peripheral precocious puberty in Li-Fraumeni syndrome: a case report and literature review of pure androgen-secreting adrenocortical tumors. J Med Case Rep 17:195. https://doi.org/10.1186/s13256-023-03889-y
27. Sugano K, Taniguchi T, Saeki M, Tsunematsu Y, Tomaru U, Shimoda T (1999) Germline p53 mutation in a case of Li-Fraumeni syndrome presenting gastric cancer. Jpn J Clin Oncol 29:513–516. https://doi.org/10.1093/jjco/29.10.513
28. Severino NP, Waisberg J, Fragoso MCBV, de Lima LGCA, Balsamo F, Henriques AC et al (2022) Rectal leiomyosarcoma as the initial phenotypic manifestation of Li-Fraumeni-like syndrome: a case report and review of the literature. J Med Case Rep 16:468. https://doi.org/10.1186/s13256-022-03671-6
29. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Rüschoff J et al (2004) Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 96:261–268. https://doi.org/10.1093/jnci/djh034
30. Goshayeshi L, Hoorang S, Hoseini B, Abbaszadegan MR, Afrazeh M, Alimardani M et al (2025) Germline variants in patients from the Iranian hereditary colorectal cancer registry. Cancer Cell Int 25:140. https://doi.org/10.1186/s12935-025-03773-3
31. Schneider K, Zelley K, Nichols KE, Schwartz Levine A, Garber J (1993) Li-Fraumeni syndrome. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A (eds) GeneReviews®. University of Washington, Seattle. https://www.ncbi.nlm.nih.gov/books/NBK1311/. Accessed 7 May 2025
32. Kumamoto T, Yamazaki F, Nakano Y, Tamura C, Tashiro S, Hattori H et al (2021) Medical guidelines for Li-Fraumeni syndrome 2019, version 1.1. Int J Clin Oncol 26:2161–2178. https://doi.org/10.1007/s10147-021-02011-w
33. Correa H (2016) Li-Fraumeni syndrome. J Pediatr Genet 5:84–88. https://doi.org/10.1055/s-0036-1579759
34. Waldmann A, Borchers P, Katalinic A (2023) Temporal trends in age- and stage-specific incidence of colorectal adenocarcinomas in Germany. BMC Cancer 23:1180. https://doi.org/10.1186/s12885-023-11660-1
35. Nichols KE, Malkin D, Garber JE, Fraumeni JF, Li FP (2001) Germ-line p53 mutations predispose to a wide spectrum of early-onset cancers. Cancer Epidemiol Biomarkers Prev 10:83–87
36. Formiga MNC, Ashton-Prolla P, Achatz MIASW (2019) Early-onset colorectal cancer in patients with Li Fraumeni syndrome: is it really enough to justify early colon cancer screening? Gastroenterology 157:264. https://doi.org/10.1053/j.gastro.2018.10.063
37. Rengifo-Cam W, Shepherd HM, Jasperson KW, Samadder NJ, Samowitz W, Tripp SR et al (2018) Colon pathology characteristics in Li-Fraumeni syndrome. Clin Gastroenterol Hepatol 16:140–141. https://doi.org/10.1016/j.cgh.2017.06.017
38. Levine AJ (2021) Spontaneous and inherited TP53 genetic alterations. Oncogene 40:5975–5983. https://doi.org/10.1038/s41388-021-01991-3
39. Pinto EM, Zambetti GP (2020) What 20 years of research has taught us about the TP53 p.R337H mutation. Cancer 126:4678–4686. https://doi.org/10.1002/cncr.33143
40. Galante PAF, Guardia GDA, Pisani J, Sandoval RL, Barros-Filho MC, Gifoni ACLVC et al (2025) Personalized screening strategies for TP53 R337H carriers: a retrospective cohort study of tumor spectrum in Li-Fraumeni syndrome adult carriers. Lancet Reg Health Am 42:100982. https://doi.org/10.1016/j.lana.2024.100982
41. Kratz CP, Achatz MI, Brugières L, Frebourg T, Garber JE, Greer MLC et al (2017) Cancer screening recommendations for individuals with Li-Fraumeni syndrome. Clin Cancer Res 23:e38–e45. https://doi.org/10.1158/1078-0432.CCR-17-0408
42. Orr BA, Clay MR, Pinto EM, Kesserwan C (2020) An update on the central nervous system manifestations of Li-Fraumeni syndrome. Acta Neuropathol 139:669–687. https://doi.org/10.1007/s00401-019-02055-3
43. Hong CS, Erson-Omay EZ, Moliterno J (2021) Multiple meningiomas arising within the same hemisphere associated with Li-Fraumeni syndrome. Surg Neurol Int 12:99. https://doi.org/10.25259/SNI_125_2019
44. Dardenne A, Dhooge M, Basset N, Chansavang A, Metras J, Farelly S et al (2025) Pathogenic germline variants in patients with early-onset colorectal cancer according to phenotype. Eur J Hum Genet 33:810–813. https://doi.org/10.1038/s41431-025-01808-x

Table

Table 1 is available in the Supplementary Files section.

Figures

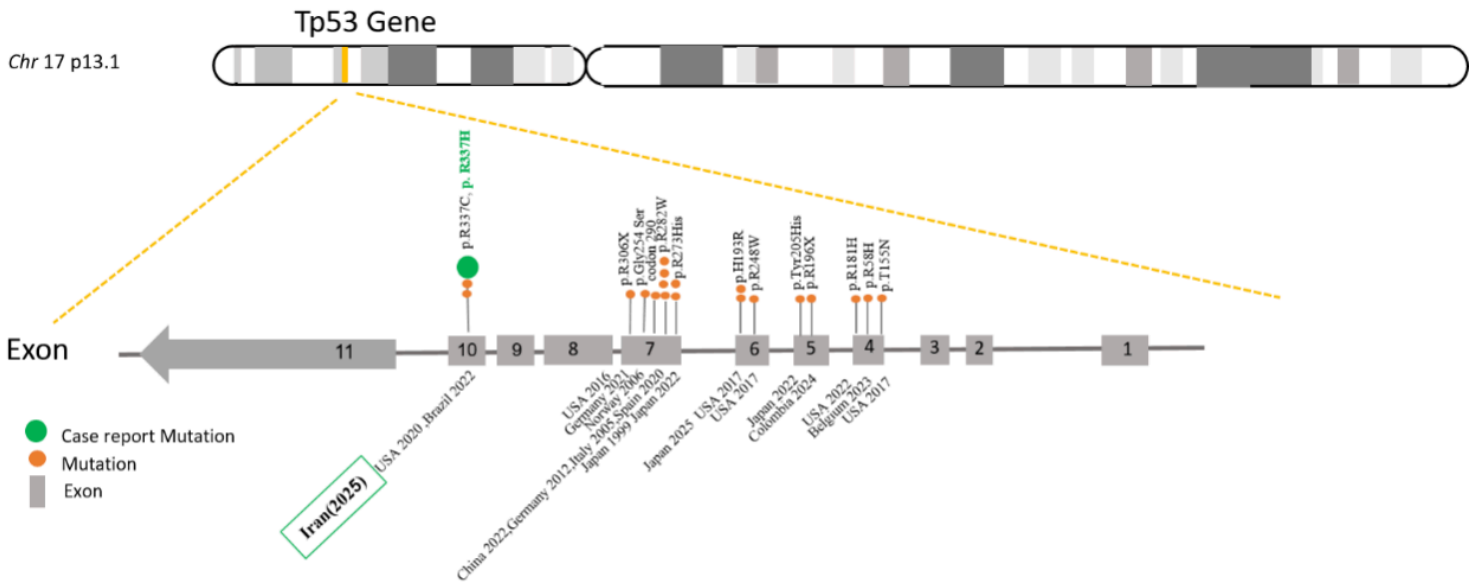


Figure 1

Distribution of pathogenic TP53 variants reported in the reviewed case reports, showing their positions across the exons and introns of the TP53 gene

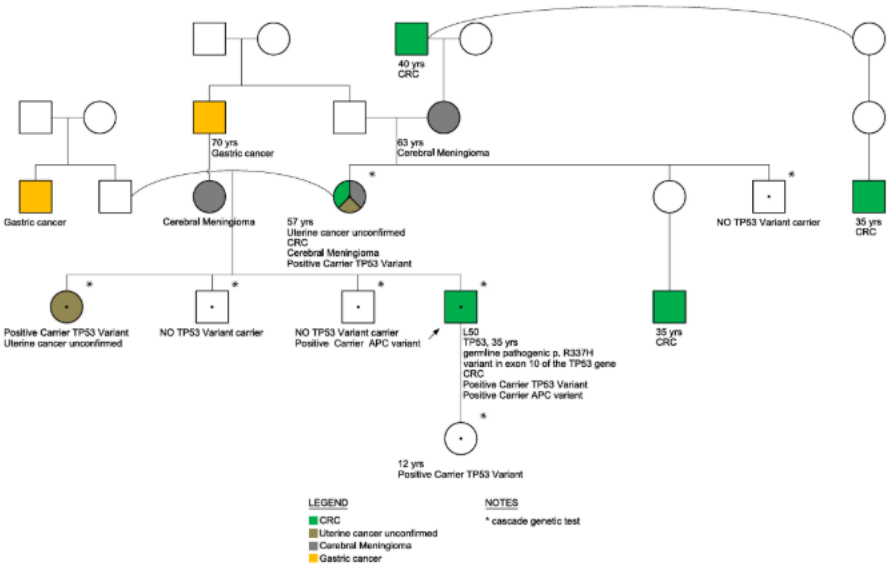


Figure 2

Schematic pedigree of the family showing cancer diagnoses and TP53 variant status. The arrow indicates the index patient. Squares represent males and circles represent females. Colors indicate reported cancer types as defined in the legend. Asterisks indicate family members who underwent cascade genetic testing

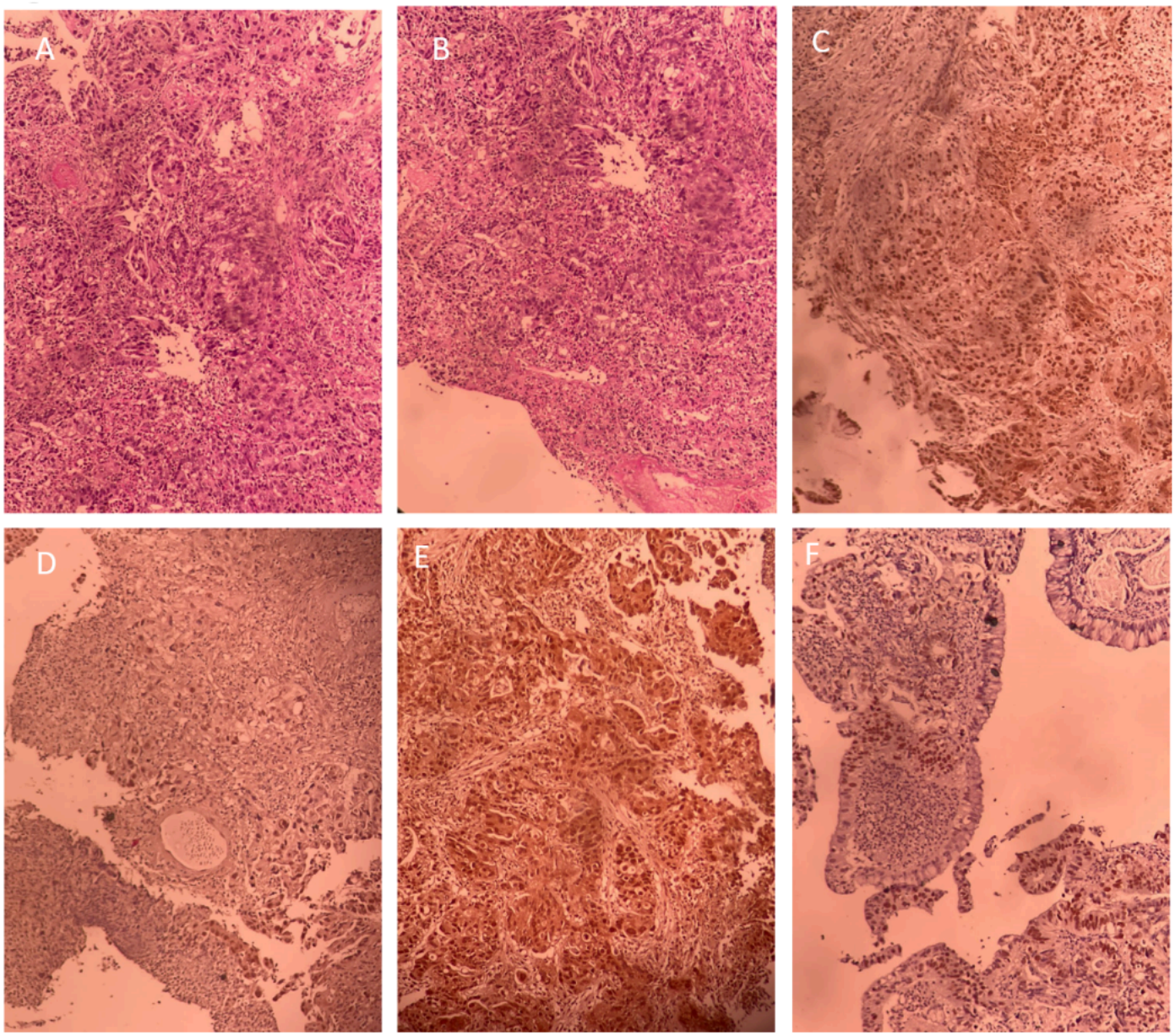


Figure 3

Histopathological and immunohistochemical analysis of rectal tumor tissue. (a, b) Hematoxylin and eosin (H&E)-stained sections showing invasive poorly differentiated rectal adenocarcinoma (×100). (c–f) Immunohistochemical staining for mismatch repair (MMR) proteins showing retained nuclear expression, consistent with a pMMR phenotype. (c) MSH2; (d) MSH6; (e) MLH1; (f) PMS2

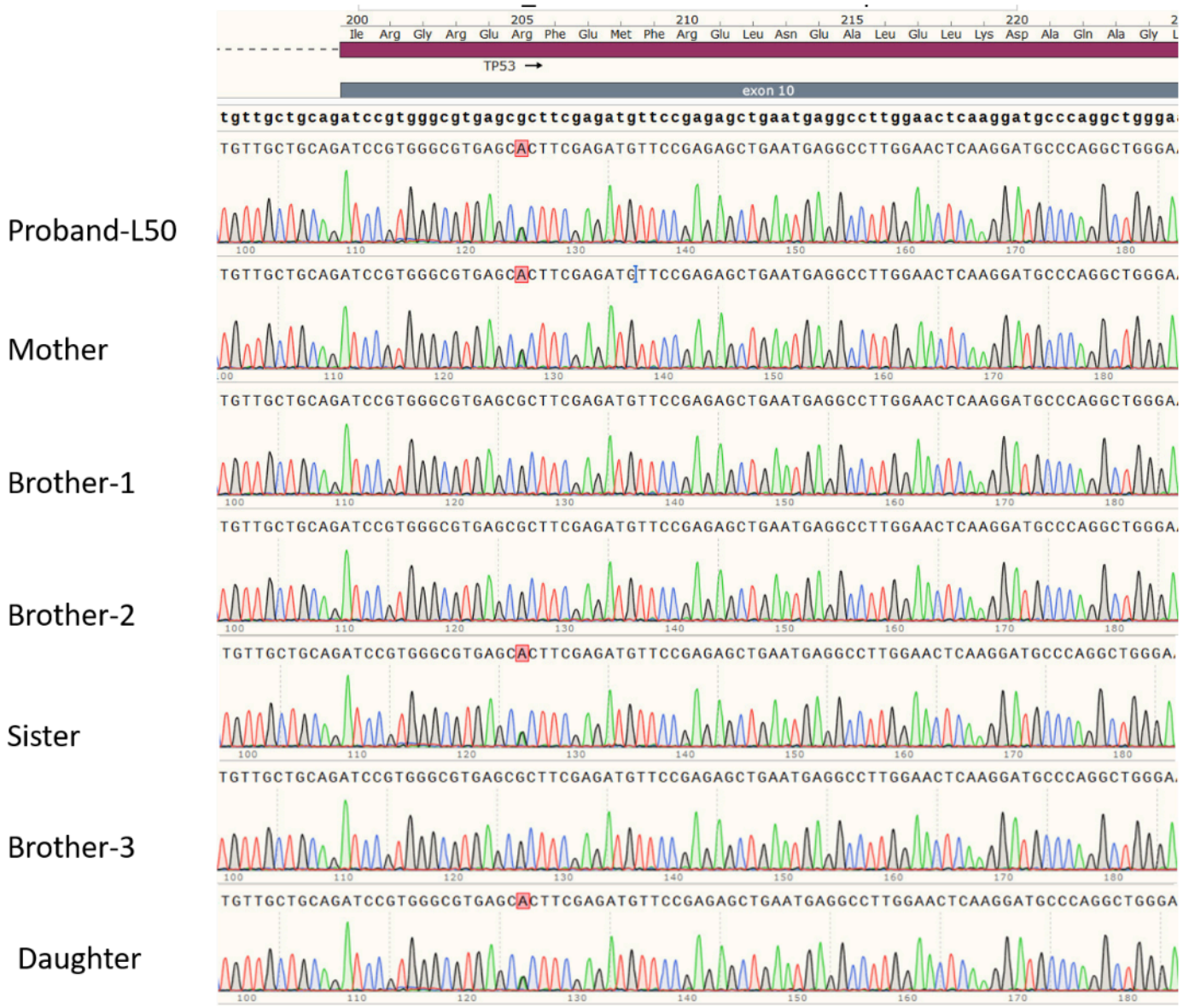


Figure 4

Representative Sanger sequencing chromatograms demonstrating the heterozygous TP53 c.1010G>A [p.(Arg337His)] variant in the index patient and variant-positive relatives. The variant position is indicated by arrows

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx