

# World Journal of *Gastroenterology*

Weekly Volume 31 Number 44 November 28, 2025



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Hu D, Yu J, Wang MX, Zhang HL. Redefining therapeutic thresholds and global guidelines: Toward precision management of intermediate-sized rectal neuroendocrine tumors. *World J Gastroenterol* 2025; 31(44): 114263 [DOI: 10.3748/wjg.v31.i44.114263]

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Zheng L, Duan SL. Neuroimmune interactions in inflammatory bowel disease: Role of intestinal macrophages and the cholinergic pathway. *World J Gastroenterol* 2025; 31(44): 109440 [DOI: 10.3748/wjg.v31.i44.109440]

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Feng YF, Su TM, Hu BB, Wang H, Li QM, Yin QB, Huang L, Liang HQ, Ren AL, Su MH, Jiang JN. Diagnostic performance of serum origin recognition complex subunit 1 protein for hepatitis B virus-related hepatocellular carcinoma. *World J Gastroenterol* 2025; 31(44): 112481 [DOI: 10.3748/wjg.v31.i44.112481]

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**Retrospective Study**

Taskiran I, Orenay-Boyacioglu S, Boyacioglu O, Erdogan IH, Culhaci N, Meteoglu I. DNA polymerase epsilon-mutant colorectal cancers: Insights into non-exonuclease domain mutation variants, microsatellite instability status, and co-mutation profiles. *World J Gastroenterol* 2025; 31(44): 112524 [DOI: 10.3748/wjg.v31.i44.112524]

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Editorial Board Member of *World Journal of Gastroenterology*, Giovanni Tarantino, MD, Professor, Senior Researcher, Department of Clinical Medicine and Surgery, Federico II University Medical School, Naples 80131, Italy. tarantin@unina.it

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The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2025 edition of Journal Citation Reports® cites the 2024 journal impact factor (JIF) for WJG as 5.4; Quartile: Q1. The WJG's CiteScore for 2024 is 8.1.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Lai Zhang*, Production Department Director: *Xiang Li*, Cover Editor: *Jia-Ru Fan*.

**NAME OF JOURNAL**

*World Journal of Gastroenterology*

**ISSN**

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

**LAUNCH DATE**

October 1, 1995

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

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<http://www.wjgnet.com/1007-9327/editorialboard.htm>

**PUBLICATION DATE**

November 28, 2025

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Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University  
Biliary Tract Disease Institute, Fudan University

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<https://www.wjgnet.com/bpg/gerinfo/242>

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## Retrospective Study

**DNA polymerase epsilon-mutant colorectal cancers: Insights into non-exonuclease domain mutation variants, microsatellite instability status, and co-mutation profiles**

Ismail Taskiran, Seda Orenay-Boyacioglu, Olcay Boyacioglu, Ibrahim Halil Erdogan, Nil Culhaci, Ibrahim Meteoglu

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade A, Grade B, Grade B, Grade B

**Novelty:** Grade A, Grade B, Grade B, Grade C

**Creativity or Innovation:** Grade A, Grade B, Grade B, Grade C

**Scientific Significance:** Grade A, Grade B, Grade B, Grade C

**P-Reviewer:** Guo WJ, PhD, Academic Fellow, China; Xu TC, MD, PhD, Professor, China

**Received:** July 30, 2025

**Revised:** September 13, 2025

**Accepted:** October 20, 2025

**Published online:** November 28, 2025

**Processing time:** 121 Days and 14.6 Hours



**Ismail Taskiran**, Department of Gastroenterology, School of Medicine, Aydin Adnan Menderes University, Aydin 09010, Türkiye

**Seda Orenay-Boyacioglu**, Department of Medical Genetics, School of Medicine, Aydin Adnan Menderes University, Aydin 09010, Türkiye

**Olcay Boyacioglu**, Faculty of Engineering, Aydin Adnan Menderes University, Aydin 09010, Türkiye

**Ibrahim Halil Erdogan, Nil Culhaci, Ibrahim Meteoglu**, Department of Pathology, School of Medicine, Aydin Adnan Menderes University, Aydin 09010, Türkiye

**Corresponding author:** Olcay Boyacioglu, PhD, Associate Professor, Faculty of Engineering, Aydin Adnan Menderes University, Merkez Kampus, Efeler, Aydin 09010, Türkiye.  
[oboyaci@adu.edu.tr](mailto:oboyaci@adu.edu.tr)

**Abstract****BACKGROUND**

Although the relationship between somatic DNA polymerase epsilon (*POLE*) exonuclease domain mutations (EDMs) and colorectal cancer (CRC) is well established, the role of *POLE* non-EDMs in CRC remains unclear.

**AIM**

To identify *POLE* non-EDMs and EDMs in CRC, and to determine their associations with accompanying mutations and microsatellite instability (MSI).

**METHODS**

In this retrospective study, next-generation sequencing was performed using a targeted colon cancer panel (Qiagen, DHS-003Z) on 356 CRC patients. Of these, 191 patients were found to carry *POLE* mutations. For these patients, MSI status was assessed using both real-time PCR (EasyPGX® Ready MSI kit) and immunohistochemistry, and accompanying somatic mutations were investigated.

**RESULTS**

*POLE* mutations were identified in 53.65% of the CRC patients. Among the *POLE*-

mutant patients, 87.96% were classified as pMMR (MSI-L), and 12.04% as dMMR (MSI-H). The most frequently observed *POLE* non-EDM variant was exon 34 c.4337\_4338delTG p.V1446fs\*3. The *POLE* EDMs were present in exon 14, with two specific variants p.Y458F (0.52%) and p.Y468N (0.52%). The most common pathogenic variants accompanying the *POLE* mutations were in *MLH3*, *MSH3*, *KRAS*, *PIK3CA*, and *BRAF* genes. *POLE* mutations were associated with a high mutational burden and MSI in CRC, particularly in the dMMR phenotype. This association suggests that *POLE* mutations may serve as important biomarkers for understanding the genetic profile of the disease and may be used in the clinical management of CRC.

## CONCLUSION

*POLE* mutations, especially non-EDMs, are frequent in MSI-L CRC and often co-occur with *MLH3*, *MSH3*, *KRAS*, *PIK3CA*, and *BRAF*, highlighting their potential role in tumor biology and as biomarkers for personalized treatment. Functional validation and multicenter studies are needed.

**Key Words:** DNA polymerase epsilon mutation; Non-exonuclease domain variants; Microsatellite instability; Colorectal cancer; Next-generation sequencing; Somatic co-mutations

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**Core Tip:** This study highlights the overlooked role of DNA polymerase epsilon (*POLE*) non-exonuclease domain mutations in colorectal cancer. By integrating next-generation sequencing with microsatellite instability testing, we show that *POLE* mutations are frequent, particularly in microsatellite-low tumors, and are often accompanied by co-mutations in *MLH3*, *MSH3*, *KRAS*, *PIK3CA*, and *BRAF*. These findings extend beyond the classical exonuclease domain hotspots, suggesting that both exonuclease and non-exonuclease *POLE* variants may serve as valuable biomarkers for prognosis and support the development of personalized treatment strategies in colorectal cancer management.

**Citation:** Taskiran I, Orenay-Boyacioglu S, Boyacioglu O, Erdogan IH, Culhaci N, Meteoglu I. DNA polymerase epsilon-mutant colorectal cancers: Insights into non-exonuclease domain mutation variants, microsatellite instability status, and co-mutation profiles. *World J Gastroenterol* 2025; 31(44): 112524

**URL:** <https://www.wjgnet.com/1007-9327/full/v31/i44/112524.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v31.i44.112524>

## INTRODUCTION

Colorectal cancer (CRC) is one of the most prevalent cancers worldwide. The genetic structure of CRCs is quite heterogeneous and exhibits different mutation profiles[1]. Within this diversity, mutations occurring in the DNA polymerase epsilon (*POLE*) gene constitute an important subgroup[2]. The *POLE* gene is located on the long arm of chromosome 12 (12q24.33) in the human genome and spans approximately 100 kb. It comprises 49 exons and encodes the catalytic subunit of the *POLE* (Pol ε) complex, which is involved in replicative DNA synthesis[1]. *POLE* is highly expressed in tissues with elevated cell proliferation, particularly during the S phase of the cell cycle. This expression pattern underscores its critical role in DNA replication and repair processes[3]. The protein encoded by this gene consists of two major functional domains: A C-terminal 3'→5' exonuclease domain (EDM) and an N-terminal DNA polymerase domain (non-EDM)[4]. Mutations in the *POLE* gene are predominantly clustered within the EDM, spanning exons 9 to 14. These mutations are associated with a hypermutated phenotype and enhanced responsiveness to immune checkpoint inhibitors[4,5]. Notably, hotspot variants such as P286R, V411 L, and S459F impair the proofreading function of the polymerase, leading to an increased mutational burden, and may contribute to the development of microsatellite-stable (MSS) tumors that are classified as microsatellite instability (MSI) negative subtypes. This conditions may affect the immunotherapy response of *POLE*-mutant CRC patients[5-7]. Non-EDM variants may also contribute to tumor development by disrupting the structural integrity and replication fidelity of DNA polymerase ε. Moreover, previous studies have reported non-EDMs in different tumor types (e.g., endometrial and CRC)[8,9] but their biological and clinical significance remains less well elucidated compared to EDMs, indicating the need for further investigations.

In *POLE*-mutant CRC, various co-mutations are also frequently observed in other genes. These co-mutations may affect the behavior of tumors and their responses to treatment[10]. For example, mutations are frequently observed in oncogenes and tumor suppressor genes such as *TP53*, *KRAS*, and *PIK3CA*. *TP53* mutations may accelerate tumor development by disrupting cell cycle control. *KRAS* mutations may affect the signaling pathways involved in cellular proliferation and differentiation[11-13].

In summary, while *POLE* EDM mutations are well characterized and associated with a high mutational burden and response to immune checkpoint inhibitors, the biological and clinical significance of non-EDM variants has been studied more limitedly. These variants, however, may influence tumor biology through potential effects on DNA replication and interactions with other co-mutations. Therefore, investigating non-EDMs in the Turkish CRC cohort provides important

and pioneering insights by revealing population-specific mutational patterns that could contribute to personalized treatment strategies. Accordingly, this study aims to comprehensively evaluate both EDM and non-EDM *POLE* mutations in the Turkish CRC cohort, along with their MSI status and associated mutational patterns. To the best of our knowledge, this is the first study to examine these relationships in this population, highlighting the potential clinical significance of *POLE* non-EDMs, a relatively underexplored mutation group in CRC.

## MATERIALS AND METHODS

### Cases

Between January 2019 and June 2024, the records of all adult patients (aged 18 and above) referred to our institutional Molecular Pathology Laboratory were retrospectively reviewed. Of the 356 consecutive patients who were diagnosed with CRC during colonoscopies performed in the gastroenterology clinic, confirmed by histopathological evaluation, underwent next-generation sequencing (NGS) gene mutation panel analysis, and had their MSI status determined, a total of 191 *POLE*-mutant CRC patients were included in the study. Although a documented family history of CRC was not available for all patients, none of the selected 191 *POLE*-mutant CRC cases exhibited clinical or genetic criteria indicative of hereditary CRC syndromes (*e.g.*, Lynch syndrome or familial adenomatous polyposis). This indicates that the selected patient cohort in our study predominantly consisted of sporadic CRC cases. Patients with missing clinical data, those for whom NGS and MSI analyses could not be performed due to technical reasons, those without *POLE* mutations, and those diagnosed with hereditary CRC syndromes were excluded from the study. The inclusion and exclusion criteria for the patients enrolled in the study are summarized in [Figure 1](#).

This study was approved by the Institutional Non-Interventional Clinical Research Ethics Committee (2024/#138), and the criteria of the Declaration of Helsinki were observed.

### DNA isolation

DNA was isolated from paraffin-embedded tissue sections (10  $\mu$ m in thickness) of the patients using the Qiagen GeneReader FFPE DNA isolation kit, following the kit's protocol, and conducted on the QIAcube (Qiagen Hilden, Germany) automated isolation device. Quantification and purity of the isolated DNA samples were conducted on a Qubit 3.0 fluorometer (Life Technologies, CA, United States).

### MSI analysis

In this study, the MSI status of the patients was evaluated using both real-time PCR and immunohistochemistry (IHC), as previously described[14].

Real-time PCR was employed to detect MSI status using the EasyPGX<sup>®</sup> Ready MSI kit, which compares the microsatellite regions in tumor tissues with those in normal tissues. This kit was used to evaluate five microsatellite loci: BAT-25, BAT-26, NR-21, NR-24, and MONO-27. Primer sequences are proprietary per the manufacturer's protocol and were not disclosed. Instability at one microsatellite locus was classified as low MSI (MSI-L), instability at two or more loci as high MSI (MSI-H), and stability at all five loci as stable MS (MSS).

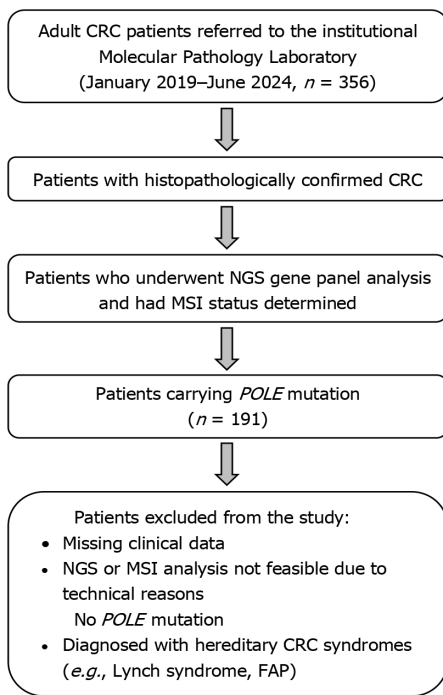
The expression of MLH1, MSH2, MSH6, and PMS2 proteins was analyzed by IHC. FFPE tissue sections were cleared with xylene, dehydrated using an alcohol series, and processed with DAKO solution at 97 °C. The sections were then incubated with the appropriate antibodies for MLH1, PMS2, MSH2, and MSH6. Analyses were performed on an Autostainer Link 48 device and antigen-antibody interactions were evaluated using diaminobenzidine. Loss of nuclear staining was checked in both internal control and tumor tissues; deficient MMR proteins (dMMR) (MLH1, MSH2, MSH6, PMS2) were accepted as MSI-H, and the presence of all proteins was accepted as a proficient MMR (pMMR).

This dual approach aligns with established guidelines and ensures accurate MSI classification.

### NGS analysis

Between 100 and 250 ng of DNA was utilized for library construction using the QIAseq Targeted DNA Human CRC Panel (#DHS-002Z, Qiagen, Hilden, Germany), which encompasses 71 genes commonly mutated in CRC. Each DNA fragment was tagged with a 12-base unique molecular index (UMI) to ensure accurate read identification. Library sequencing was carried out on the Illumina MiniSeq system (Illumina Inc., San Diego, CA, United States) employing a 2  $\times$  150 bp paired-end format. According to the kit configuration, the MiniSeq platform yields approximately 7.5-8 million reads in mid-output mode and up to 25 million reads in high-output mode. In the present study, sequencing parameters were adjusted to obtain an average on-target coverage depth of  $\geq 250 \times$  for tumor samples, with each case achieving a minimum overall coverage of 30  $\times$ . Raw reads were subsequently aligned to the GRCh37 (hg19) human reference genome.

Variant detection, annotation, scoring, and filtering were conducted using the QIAseq Targeted Panel Analysis plug-in designed specifically for this panel and operated *via* the Biomedical Genomics Workbench v5 software (Qiagen, Valencia, CA, United States). To enhance variant reliability, a stepwise filtering pipeline was applied: Confidence filter: Variants commonly found in public reference databases (Allele Frequency Community, 1000 Genomes Project, ExAC, NHLBI ESP) were excluded. Quality filter: Variants with a call quality below 20 or with a population frequency greater than 0.5% were removed. Genetic filter: Only pathogenic/potentially pathogenic and loss-of-function alterations (*e.g.*, frameshift, nonsense) were retained, and the UMI-based variant allele frequency (VAF) was restricted to the 1%-45% range. For downstream interpretation of somatic mutations, the R/Bioconductor package maftools was employed, while mutation



**Figure 1 Selection process of the colorectal cancer patients.** CRC: Colorectal cancer; NGS: Next-generation sequencing; *POLE*: DNA polymerase epsilon; MSI: Microsatellite instability.

distribution patterns were visualized using the ggplot2 Library. Variants were divided into four categories according to cancer diagnosis, prognosis, and treatment effects.

### Statistical analysis

Analysis of the data was performed using SPSS 22.0 (IBM, Armonk, NY, United States).  $\chi^2$  test was utilized for comparing the categorical data. The significance level was set at  $P < 0.05$ . The results are presented as numbers and percentages.

## RESULTS

A *POLE* mutation was observed in 191 (53.65%) of 356 CRC patients. All clinical and pathological features of *POLE*-mutant CRC patients are presented in [Table 1](#).

The most frequently observed variation in the *POLE* gene in patients was the non-EDM variant exon 34 c.4337\_4338delTG p.V1446fs\*3 (conflicting classifications of pathogenicity), identified in 182 patients (95.29%) ([Table 2](#)). Other observed *POLE* non-EDM variants in the patients included p.D612N (0.52%), p.R1909 (0.52%), p.N518fs\*10 (0.52%), p.Q1774\* (0.52%), p.Q911\* (0.52%), p.A1885T (0.52%), and p.L1171fs\*6 (0.52%). *POLE* EDM (exons 9-14) mutations were rare, and only p.Y458F (0.52%) and p.Y468N (0.52%) variants located in exon 14 were detected in patients ([Table 2](#)).

The most frequent mutations accompanying *POLE* mutations were in the *MLH3* (72.25% in non-EDM, 100% in EDM) and *MSH3* (72.25% in non-EDM, 50% in EDM) genes, followed by *KRAS* (41.36%), *PIK3CA* (14.66%), *BRAF* (6.81%), *PMS2* (5.76%), *TP53* (5.76%), *MSH6* (5.24%), *ERCC5* (5.24%), and *TCF7 L2* (5.24%) in non-EDM cases ([Figure 2](#)). All gene variations accompanying *POLE* mutations in the cohort are presented in [Table 3](#).

In the MSI evaluation of *POLE*-mutant patients, IHC revealed that 168 cases (87.96%) were pMMR (MSI-L) and 23 cases (12.04%) were dMMR (MSI-H), whereas Real-time PCR classified 165 cases as MSI-L, 8 cases as MSS, and 18 cases as MSI-H. Concordance analysis demonstrated a good level of agreement between the two methods (Cohen's kappa = 0.77). The observed discrepancies were primarily attributed to limitations in FFPE tissue quality and variability in tumor cell content.

We performed Fisher's exact test to compare MSI-H frequency between *POLE* EDM and non-EDM groups ([Table 4](#)). No statistically significant difference was observed ( $P = 1.0$ ).

[Table 5](#) provides stratified descriptive statistics of *POLE*-mutant CRC patients by age, tumor location, and MSI status, including the most frequent co-mutations. EDM mutations were extremely rare ( $n = 2$ ), whereas the majority of *POLE* mutations were non-EDM ( $n = 189$ ). Among *POLE*-mutant patients, MSI-H was observed in 23 cases (12.04%), primarily among non-EDM mutations. *POLE* mutations were more common in the colon than in the rectum across all MSI categories. Age stratification showed that most patients were between 50-65 years old. The estimated odds ratio (OR) for MSI-H in EDM *vs* non-EDM cases was 0.03 (95%CI: 0.001-1.2,  $P = 0.06$ ), highlighting the low prevalence of EDM mutations and the need for cautious interpretation. Co-mutation patterns, most frequently *MLH3*, *MSH3*, *KRAS*, *PIK3CA*, *BRAF*, *PMS2*, *TP53*, *MSH6*, *ERCC5*, and *TCF7 L2*, were mainly observed in non-EDM cases.

**Table 1 Clinical and pathological features of DNA polymerase epsilon-mutant colorectal cancer patients, n (%)/mean ± SD**

Characteristics	Value
Gender <sup>a</sup>	
Female	69 (36.13)
Male	122 (63.87)
Age at diagnosis, years	mean ± SD
Female	63.6 ± 12.3
Male	66.6 ± 10.2
All <i>POLE</i> -mutant CRC patients	65.5 ± 11.1
Differentiation degree <sup>a</sup>	
Well differentiated	80 (41.88)
Moderately differentiated	73 (38.22)
Poorly differentiated	38 (19.90)
Localization <sup>a</sup>	
Colon	160 (83.77)
Rectum	31 (16.23)

<sup>a</sup>*P* < 0.01.CRC: Colorectal cancer; *POLE*: DNA polymerase epsilon.**Table 2 The DNA polymerase epsilon exonuclease domain mutations and non-exonuclease domain mutations observed in colorectal cancer patients**

<i>POLE</i> mutation	Exon	Nucleotide substitution	Protein change	Mutation type	Clinical significance
Non-EDM	34	c.4337_4338delTG	p.V1446fs*3	Microsatellite (frameshift)	Conflicting classifications of pathogenicity
EDM	14	c.1373A>T	p.Y458F	Nonsense	Pathogenic
EDM	14	c.1402T>A	p.Y468N	Missense	Uncertain significance
Non-EDM	17	c.1834G>A	p.D612N	Missense	Uncertain significance
Non-EDM	42	c.5725C>T	p.R1909	Nonsense	Pathogenic
Non-EDM	15	c.1551delC	p.N518fs*10	Deletion	Pathogenic
Non-EDM	41	c.5653G>A	p.A1885T	Frameshift	Uncertain significance
Non-EDM	29	c.3510dupA	p.L1171fs*6	Duplication	Pathogenic
Non-EDM	39	c.5320C>T	p.Q1774*	Nonsense	Pathogenic
Non-EDM	24	c.2731C>T	p.Q911*	Nonsense	Pathogenic

EDM: Exonuclease domain mutation; *POLE*: DNA polymerase epsilon.

## DISCUSSION

This study is the first to investigate *POLE* EDMs, non-EDMs, and accompanying mutations in Turkish patients with CRC, along with the MSI status of patients.

*POLE* mutations are generally considered significant genetic findings in various cancer types, including CRC. Over the past decade, studies have reported that somatic mutations in the *POLE* gene occur in 1%-12.3% of CRC cases, while *POLE* EDMs are present in only 1%-2% of cases[8,10,15]. For instance, Domingo *et al*[15] reported *POLE* mutations in only 1% of CRC patients, and similarly, Guo *et al*[10] found a 1.5% prevalence of *POLE* mutations in a Chinese CRC cohort. Both studies emphasized that these mutations contribute significantly to the genetic profile of the disease and are associated with a high mutational burden. The most notable finding in the present study was that *POLE* mutations were detected in 53.65% of CRC patients in the Turkish cohort, a proportion considerably higher than that reported in other populations.

Table 3 Variants accompanying DNA polymerase epsilon mutations in colorectal cancer patients

<b>POLE mutations</b>	<b>Gene</b>	<b>Nucleotide substitution</b>	<b>Protein change</b>
	<i>APC</i>	c.994C>T, c.646C>T, c.4348C>T, c.1690C>T, c.4192_4193delAG, c.4729G>T	p.R332*, p.R216*, p.R1450*, p.R564*, p.R1399fs*9, p.E1577*
	<i>ASXL1</i>	c.1188_1201delGCGTGGTGGT	p.Q396fs*9
	<i>AXIN2</i>	c.1195C>T	p.R399*
	<i>BAX</i>	c.763A>T, c.121dupG	p.I255F, p.E41fs*33
	<i>BLM</i>	c.1544delA	p.N515fs*16
	<i>BRAF</i>	c.1742A>T, c.2141T>A, c.1799T>A, c.2102G>T, c.1406G>C, c.1790T>A	p.N581I, p.I714N, p.V600E, p.R701I, p.G469A, p.L597Q
	<i>BRCA1</i>	c.1961delA, c.66dupA	p.K654fs*47, p.E23fs*18
Non-EDM	<i>BRCA2</i>	c.1813delA, c.5073delA, c.7007G>A, c.9072_9092delCAAC, c.9097delA	p.I605fs*9, p.K1691fs*15, p.R2336H, p.N3024_T3030, p.T3033fs*29
	<i>CDH1</i>	c.549_554delCAAAGA, c.944dupA	p.D183 K184del, p.N315fs*6
	<i>CEBPA</i>	c.564_566delGCC	p.P189del
	<i>CHEK2</i>	c.1556C>T, c.562C>T	p.T519M, p.R188W
	<i>CREBBP</i>	c.5837delC	p.P1946fs*30
	<i>EGFR</i>	c.2236_2250delGAATTAAG, c.2174C>T, c.2509G>A	p.E746_A750del, p.T725M, p.D837N
	<i>EP300</i>	c.4408delA, c.6370dupG, c.4408delA, c.1425dupT	p.M1470fs*26, p.V2124fs*86, p.M1470fs*26, p.Q476fs*37
	<i>ERBB2</i>	c.2524G>A	p.V842I
	<i>ERCC5</i>	c.2751delA	p.K917fs*65
	<i>FBXW7</i>	c.1436G>A	p.R479Q
	<i>FGFR1</i>	c.396_398delTGA	p.D133del
	<i>FGFR3</i>	c.1148delA, c.2128G>A, c.1150T>C	p.F383S, p.G710S, p.F384 L
	<i>FLT4</i>	c.1267delC	p.Q423fs*70
	<i>IDH1</i>	c.394C>T	p.R132C
	<i>IDH2</i>	c.419G>A	p.R140Q
	<i>JAK2</i>	c.515G>A	p.R172Q
	<i>JAK3</i>	c.1849G>T	p.V617F
	<i>KIT</i>	c.1880C>T, c.2447A>T	p.P627 L, p.D816V
	<i>KRAS</i>	c.38G>A, c.35G>C, c.182A>G, c.35G>A, c.35G>T, c.351A>C	p.G13D, p.G12A, p.Q61R, p.G12D, p.G12V, p.K117N
	<i>MLH1</i>	c.676C>T	p.R226*
	<i>MLH3</i>	c.2116delA, c.1755delA	p.T706fs28, p.E586fs*24
	<i>MSH3</i>	c.1148delA	p.K383fs*32
	<i>MSH6</i>	c.2314C>T, c.3261dupC	p.R772W, p.F1088fs*32
	<i>NRAS</i>	c.34G>T, c.182A>T, c.35G>A, c.38G>A	p.G12C, p.Q61 L, p.G12D, p.G13D
	<i>PALB2</i>	c.3201+1G>A	p.?
	<i>PIK3CA</i>	c.1634A>G, c.3140A>T, c.331A>G	p.E545G, p.H1047 L, p.K111E
	<i>PIK3R1</i>	c.244delA, c.1690A>G	p.I82fs*32, p.N564D
	<i>PMA2</i>	c.1239delA	p.D414fs*34
	<i>PMS2</i>	c.1239delA, c.630dupA	p.D414fs*34, p.R211fs*38
	<i>POLD1</i>	c.347delC	p.P116fs*53
	<i>POLD3</i>	c.898delA	p.R300fs*5

<i>PTEN</i>	c.19G>T, c.407G>A, c.802-2delA, c.802-2A>T, c.397G>A	p.E7*, p.C136Y, p.?, p.?, p.V133I
<i>RET</i>	c.1900T>A	p.C634S
<i>SMAD4</i>	c.1094G>T	p.G365V
<i>TCF7 L2</i>	c.1385delA, c.1403delA	p.K462fs*23, p.K468fs*23
<i>TGFBR2</i>	c.383dupA	p.P129fs*3
EDM	<i>MLH3</i> c.2116delA, c.1755delA	p.T706fs28, p.E586fs*24
	<i>MSH3</i> c.1148delA	p.K383fs*32

?: Unknown.

**Table 4 Distribution of DNA polymerase epsilon mutation type and microsatellite instability status**

<i>POLE</i> mutation type	Total patients (n)	MSI-H (n)	MSS/MSI-L (n)	P value
EDM mutation	2	0	2	
Non-EDM mutation	189	23	166	
Total	191	23	168	P = 1.0

EDM: Exonuclease domain mutation; MSI-H: High microsatellite instability; MSI-L: Low microsatellite instability; MSS: Microsatellite-stable; *POLE*: DNA polymerase epsilon.

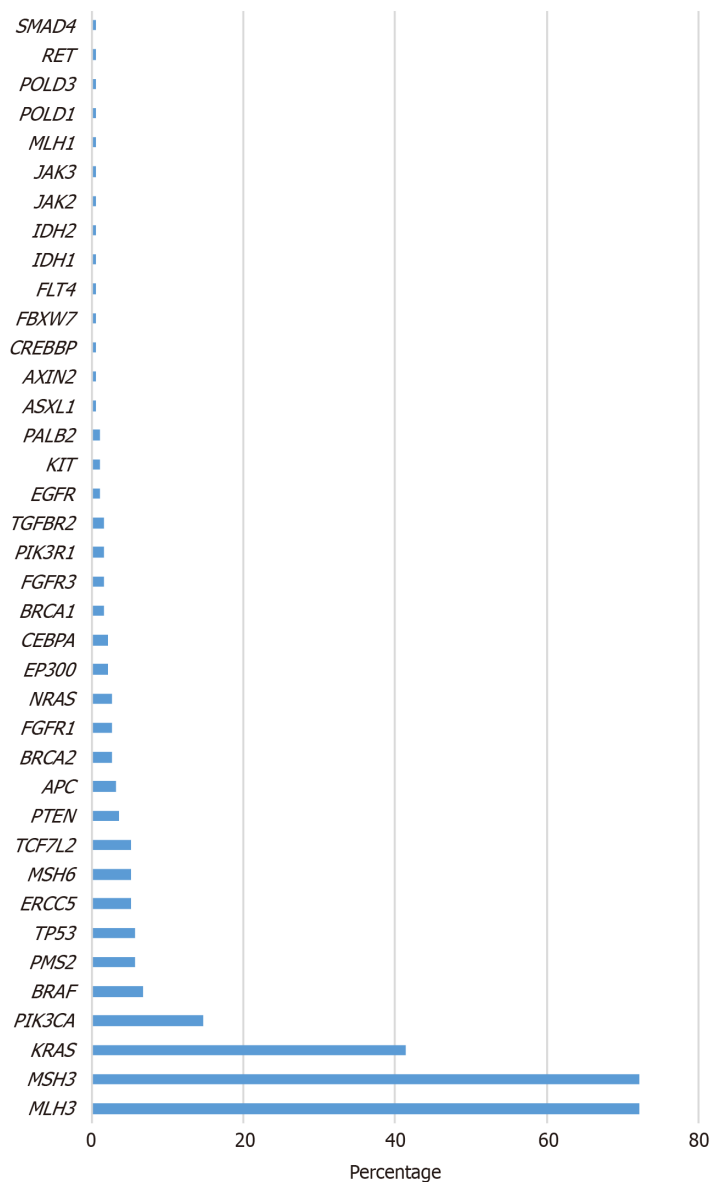
**Table 5 Stratified descriptive statistics of DNA polymerase epsilon-mutant colorectal cancer patients by age, tumor location, and microsatellite instability status, including all co-mutations, n (%)**

<i>POLE</i> mutation	Patient (n)	MSI-H	MSS/MSI-L	Co-mutation	OR MSI-H	95%CI	Colon (n)	Rectum (n)	Age (n)		
									< 50 years	50-65 years	> 65 years
EDM	2	0 (0)	2 (100)	-	0.03	0.001 to -1.2	2	0	1	1	0
Non-EDM	189	23 (12.17)	166 (87.83)	<i>BRAF, ERCC5, KRAS, MLH3, MSH3, MSH6, PIK3CA, PMS2, TCF7 L2, TP53</i>	1 (reference)	-	150	39	50	100	39
Total	191	23 (12.04)	168 (87.96)	-	-	-	152	39	51	101	39

The most frequent 10 co-mutations are listed. CI: Confidence interval; EDM: Exonuclease domain mutation; MSI: Microsatellite instability; MSI-H: High microsatellite instability; MSI-L: Low microsatellite instability; MSS: Microsatellite-stable; OR: Odds ratio; *POLE*: DNA polymerase epsilon.

However, this high prevalence is largely driven by a single variant (p.V1446fs\*3). When this variant is excluded from the analysis, the prevalence decreases to 2.53%, aligning more closely with the range reported in the literature (approximately 1%-12%). Therefore, the elevated *POLE* frequency observed in our study predominantly reflects the impact of a single variant with uncertain pathogenicity. Furthermore, the preferential use of NGS in patients with advanced-stage disease or suspected molecular alterations increases the risk of referral bias. Analytical factors (panel design, targeted regions, sequencing depth, and VAF thresholds) and population-specific genetic differences may also contribute to the observed high prevalence. These factors are not mutually exclusive and may act in combination. Accordingly, our findings should be interpreted with caution and validated in larger, multicenter cohorts.

Although there is insufficient evidence to support the pathogenic role of *POLE* non-EDMs, some studies have validated their pathogenic effects[16]. Stenzinger *et al*[8] identified somatic *POLE* non-EDMs in 12.3% of sporadic MSS CRC cases, and another study reported *POLE* non-EDMs in 3%-4% of CRC and endometrial cancers[9]. Consistent with the literature, our study found a *POLE* EDM rate of approximately 1%, whereas the frequency of *POLE* non-EDMs was higher than previously reported. As previously noted, this elevated rate may be attributed to referral bias, methodological differences, and potential population-specific genetic variations. In this study, the most frequently observed variant was the exon 34 c.4337\_4338delTG p.V1446fs\*3 frameshift variant, classified as having 'Conflicting classifications of pathogenicity.' This specific mutation has not been previously reported in CRC patients. Previous studies, such as Stenzinger *et al*[8] and



**Figure 2** Genes mutated alongside DNA polymerase epsilon mutations in colorectal cancer patients.

Briggs *et al*[9], have reported different non-EDM mutations in CRC and endometrial cancer cohorts. This mutation represents the first *POLE* non-EDM variant with a high incidence in Turkish CRC patients and is generally associated with a high mutational burden. Our study also reports the frequency of other *POLE* non-EDM and EDM variants, and understanding the pathogenic effects of these variants is particularly important for informing therapeutic approaches. While our findings expand the mutational spectrum of *POLE* in CRC, larger-scale studies including different Turkish CRC subgroups, as well as functional analyses (such as *in vitro* expression, cell proliferation/apoptosis assays, and replication error/DNA repair efficiency tests) are warranted to clarify the biological impact and generalizability of this variant.

Excluding potentially recurrent mutations in CRC, other distinct variants have also been listed in the literature for *POLE*. Most of these variants are present in the EDM and include mutations, such as p.W347C, p.N363Ks, p.D368V, p.K425R, p.P436S, and p.Y458F[17]. Among them, p.D368V and p.Y458F were functionally verified[18-22]. In the current study, *POLE* EDMs identified in patients included the p.Y458F and p.Y468N variants. The p.Y458F variant has been classified as a class 5 pathogenic variant of CRC, as reported by Rocque *et al*[23]. The p.Y468N variant (classified as "uncertain significance") identified in our patients represents the first reported *POLE* EDM in the Turkish population. However, the frequency of EDMs was lower than that of the non-EDMs. This discrepancy could be due to population differences and the limited number of studies that detected non-EDMs.

The incidence of somatic *POLE* mutations has been reported to be higher in patients with colon cancer than in those with rectal cancer[24,25]. Similarly, in our study, the mutation incidence was higher in colon cancer, which is consistent with the literature.

Two methods are generally used for MSI detection: First, molecular analysis of MSI markers by PCR; and second, evaluation of the expression of four MMR proteins in histological sections by IHC. In the literature, discordances between

these two methods have been rarely reported, particularly in cases with mutations in MMR proteins, *POLE* mutations, or *MLH1* promoter methylation, where IHC results may be inconclusive[26-30]. In such cases, molecular MSI testing is recommended for confirmation[14]. In our study, concordance between IHC and PCR results was assessed using Cohen's kappa, which was calculated as 0.77, indicating a "good level of agreement" between the two methods. In most discordant cases, differences in sample quality and tumor cell content were the main contributing factors. These findings are consistent with the high concordance rates reported in the literature and support the complementary use of both IHC and molecular testing for MSI detection.

The frequency of dMMR/MSI-H tumors in patients with CRC is approximately 15%-20%, with stage IV dMMR/MSI-H tumors representing only 2%-4% of all metastatic CRC cases[31]. In our study, a similar rate was observed, with 12.04% of CRC patients showing a dMMR/MSI-H status, which is consistent with literature.

The identification of 87.96% of *POLE*-mutant patients as having MSI-L indicates a strong association between these mutations and MSI-L. Carethers *et al*[31], *POLE* mutations are typically associated with an ultra-mutated phenotype but not necessarily with MSI-H, which is consistent with our finding that most *POLE*-mutant tumors were MSI-L. In our study, no statistically significant association was observed between MSI status and EDM or non-EDM mutations. This finding is likely due to the insufficient number of patients with EDM mutations.

In our cohort, the frequent co-occurrence of *POLE* mutations with variants in *MLH3*, *MSH3*, *KRAS*, *PIK3CA*, and *BRAF* is noteworthy. These co-mutation patterns point to several possible biological mechanisms. DNA repair pathways (MMR genes: *MLH3*, *MSH3*, *PMS2*, *MSH6*): Co-mutations in these genes, together with *POLE* alterations, may exacerbate DNA repair deficiencies, driving tumors toward an ultra-mutated phenotype. This may, in turn, enhance sensitivity to immune checkpoint inhibitors[2,15,16,24]. Oncogenic signaling pathways (*KRAS*, *PIK3CA*, *BRAF*): Mutations in the MAPK and PI3K/AKT pathways, when combined with the mutational burden induced by *POLE* alterations, may increase immunogenicity and tumor heterogeneity[30,31]. Tumor suppressor genes (*TP53*, *PTEN*, *SMAD4*): Additional mutations in these genes may contribute to loss of cell cycle control and the development of a more aggressive tumor phenotype[15,31]. These patterns indicate that *POLE* mutations shape tumor biology not in isolation, but in concert with co-mutations. Clinically, such combinatorial mutation profiles may help to identify patient subgroups most likely to benefit from immunotherapy and may guide the discovery of novel therapeutic targets[16,24,30]. Specifically, the DNA mismatch repair (MMR) genes *MLH3* and *MSH3*, when present alongside *POLE* mutations, are suggested to further impair DNA repair capacity, potentially increasing tumor mutational burden (TMB) and genomic instability[22,32]. CRC-specific studies have demonstrated that *POLE* mutations, particularly EDMs combined with *MLH3/MSH3* mutations, are associated with high TMB and MSI-H phenotypes[32,33]. Although data on non-EDM *POLE* mutations are more limited, recent CRC studies have reported that these variants, when occurring together with MMR genes, may also exacerbate DNA repair deficiencies and contribute to MSI-like phenotypes in certain subgroups[34,35]. Therefore, not only EDMs but also non-EDM mutations may have potential biological significance in the presence of *MLH3/MSH3* co-mutations. In conclusion, although survival data were not available in our study, the literature suggests that *POLE* mutations in CRC - particularly when co-occurring with *MLH3/MSH3* - may increase DNA repair deficiencies, elevate TMB, and influence sensitivity to immunotherapy. In light of these findings, it is reasonable to propose the hypothesis that *POLE* mutations accompanied by *MLH3/MSH3* alterations may further impair DNA repair capacity not only in the presence of EDM variants but also when non-EDM variants are involved. The co-occurrence of *POLE* + *MLH3/MSH3* observed in our study may be better explained by a model that includes contributions from non-EDMs, rather than being limited to classical EDM variants. However, the uncertainties regarding the pathogenic impact of non-EDM variants and their contribution to DNA repair deficiency highlight the need for further biological investigations in this area. In particular, large CRC-specific genomic sequencing datasets (*e.g.*, TCGA-COADREAD, MSK-CRC panels) should be systematically analyzed to assess the prevalence of non-EDM *POLE* variants, their co-mutation distribution, impact on TMB, and associations with survival and treatment response.

Our study not only highlights the high frequency of *POLE* mutations but also emphasizes the importance of their associated co-mutation profiles. Evaluating *POLE* mutations in conjunction with MSI status and co-mutations may help better identify candidates for immunotherapy[15,16]. Although the pathogenic effects of *POLE* non-EDMs have not been fully established, their high prevalence observed in our study suggests potential impacts on CRC biology. The frequent co-occurrence of these mutations with key genes may influence tumor immunogenicity and supports the exploration of combination therapeutic approaches (*e.g.*, immunotherapy plus targeted therapies)[26]. Even without functional validation, these findings provide a foundation for future studies aimed at assessing the prognostic and therapeutic significance of non-EDMs.

### Limitations

This study is subject to several important limitations. The apparently high prevalence of *POLE* mutations (53.65%) was primarily driven by a single variant of uncertain pathogenicity (p.V1446fs3); exclusion of this variant reduced the prevalence to 2.53%. Additional factors such as referral bias, differences in NGS panels, and population-specific genetic features may also have contributed. Due to its retrospective design, stage-specific analyses of *POLE* mutation frequency could not be performed. Furthermore, the very limited number of patients carrying EDM variants posed a significant restriction in assessing associations between *POLE* mutations and clinicopathological parameters. The cohort consisted exclusively of CRC patients from a single institution in Türkiye, which further limits the external generalizability of the findings. Importantly, the functional impact of *POLE* non-EDM variants was not experimentally validated in this study. Of note, the most frequent variant (p.V1446fs3) has been inconsistently classified regarding pathogenicity, underscoring the need for functional validation through approaches such as cell culture and DNA repair assays. The relatively small size of the *POLE*-mutant subgroup, together with the limited MSI-H subset, weakened the power of subgroup and stratification analyses. In particular, the presence of only two patients harboring EDM variants rendered stratified evaluations

underpowered. Therefore, these findings should be interpreted with caution. To strengthen the evidence base, multicenter studies or pooled data approaches (*e.g.*, meta-analyses) are warranted. Finally, long-term clinical outcomes such as disease-free survival and treatment response could not be assessed, due to the retrospective nature of the study and incomplete follow-up data. This limitation precluded evaluation of the prognostic and therapeutic implications of POLE mutations-particularly non-EDM variants-and restricts their current clinical utility.

## CONCLUSION

In this study, POLE mutations, particularly non-EDM variants, were highly prevalent in a Turkish CRC cohort, mostly in MSI-L tumors. The most frequent non-EDM variant (exon 34 c.4337\_4338delTG p.V1446fs\*3) has unverified pathogenicity and unknown functional impact. POLE mutations often co-occurred with *MLH3*, *MSH3*, *KRAS*, *PIK3CA*, and *BRAF*, potentially exacerbating DNA repair deficiencies and affecting tumor biology. These findings suggest that both EDM and non-EDM POLE variants may play an important role in CRC and could serve as potential biomarkers; functional validation and multicenter studies are needed to clarify the pathogenic effects of non-EDM variants.

## FOOTNOTES

**Author contributions:** Taskiran I, Orenay-Boyacioglu S, Boyacioglu O, Erdogan IH, Culhaci N and Meteoglu I conceptualized and designed the study; Orenay-Boyacioglu S, Boyacioglu O and Erdogan IH performed the investigation and formal analysis; Taskiran I, Orenay-Boyacioglu S, Boyacioglu O, Erdogan IH, Culhaci N and Meteoglu I contributed to methodology and project administration; Taskiran I provided resources; Taskiran I, Orenay-Boyacioglu S, Boyacioglu O, Erdogan IH, Culhaci N and Meteoglu I supervised the work; Orenay-Boyacioglu S, Boyacioglu O and Erdogan IH prepared the original draft; Taskiran I, Orenay-Boyacioglu S, Boyacioglu O, Erdogan IH, Culhaci N and Meteoglu I reviewed and edited the manuscript; all authors have read and approved the final manuscript.

**Institutional review board statement:** This study was approved by the Aydin Adnan Menderes University Non-Interventional Clinical Research Ethics Committee (2024/#138). The Helsinki Declaration criteria were also followed.

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** The authors declare no conflicts of interest.

**Data sharing statement:** All relevant data are included in the manuscript. Materials, data, and protocols described within the paper are available upon reasonable request to the corresponding author.

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**Country of origin:** Türkiye

**ORCID number:** Olcay Boyacioglu 0000-0003-0436-3020.

**S-Editor:** Li L

**L-Editor:** A

**P-Editor:** Wang CH

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