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Prevalence and clinical significance of rs9929218 in *Cadherin 1* and rs6983267 in the 8q24 region among Kurdish colorectal cancer patients in Iraq

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Abstract

Colorectal cancer (CRC) is a leading cause of cancer morbidity and mortality worldwide, with genetic factors playing a significant role in its pathogenesis. This study investigated the prevalence of two single-nucleotide polymorphisms (SNPs) – rs9929218 in the *Cadherin 1* (*CDH1*) gene and rs6983267 in the 8q24 region – among Kurdish CRC patients in Sulaymaniyah, Iraq, and assessed their association with clinicopathological features. Blood samples from 290 CRC patients and 100 healthy controls were analyzed using allele-specific polymerase chain reaction. The frequency of rs9929218 was 20.34% in CRC patients compared to 7% in controls, while rs6983267 was detected in 26.55% of CRC cases versus 11% of controls. Both SNPs were significantly associated with CRC risk in univariate analyses; however, after adjusting for age, sex, tumor grade, and TNM stage in multivariate logistic regression, neither SNP remained an independent risk factor. Nonetheless, both SNPs showed significant associations with advanced tumor stage, nodal involvement, and perineural invasion, suggesting a potential role in disease progression rather than initiation. These findings enhance the understanding of CRC genetics in the Kurdish population and highlight the need for larger, functionally validated studies to confirm these associations.

Keywords: Colorectal cancer; Genetic polymorphism; *CDH1* gene; 8q24 region; Cancer susceptibility; Kurdish population

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1. Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related morbidity and mortality worldwide, with significant geographical and ethnic variations in its incidence and genetic predisposition. In 2020 alone, CRC accounted for approximately 10% of global cancer cases and deaths, making it the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths.[1] The identification of genetic markers associated with CRC risk has been a focal point of cancer research, aiming to enhance early detection, prevention, and personalized treatment strategies.[2] Among the numerous genetic variants studied, single-nucleotide polymorphisms (SNPs) have emerged as critical factors influencing CRC susceptibility.[3] The SNP rs9929218 in the

Cadherin 1 (*CDH1*) gene and rs6983267 in the 8q24 region are two such variants that have garnered considerable attention.[4,5]

The *CDH1* gene encodes E-cadherin, a protein essential for cell-cell adhesion and the maintenance of epithelial integrity. Mutations and polymorphisms in *CDH1* have been implicated in various cancers, including CRC, due to their role in tumor progression, invasion, and metastasis. Specifically, rs9929218 has been associated with an increased risk of colorectal adenomas and cancer. This variant may influence the expression or function of E-cadherin, thereby contributing to tumorigenesis.[6,7] As a biomarker, rs9929218 holds potential for identifying individuals at higher risk for CRC and for informing tailored prevention strategies.[8]

The 8q24 region, often described as a "gene desert," lacks protein-coding genes but contains regulatory elements that influence the expression of nearby oncogenes, such as *MYC*. The SNP rs6983267, located in this region, has been robustly linked to an elevated risk of several cancers, including CRC.[9,10] Functional studies suggest that the G allele of rs6983267 enhances the binding of transcription factors, such as TCF7L2, leading to increased MYC expression and subsequent tumorigenesis.[11] In addition, rs6983267's role in long-range chromatin interactions underscores the importance of non-coding regulatory regions in cancer genetics. The association of this SNP with CRC highlights the potential for targeting non-coding elements in future therapeutic interventions.[12]

Recent studies highlight the necessity of population-specific research to enhance our understanding of the genetic epidemiology of CRC.[13-16] While polymorphisms such as rs9929218 and rs6983267 have been extensively investigated, their prevalence and impact vary across ethnic groups, and data remain limited for several populations.[15] Most genetic association studies have predominantly focused on European and East Asian populations,[16] leaving the genetic landscape of understudied groups, such as the Kurdish population, largely unexplored.

The Kurdish population, characterized by its unique genetic background and potential founder effects, presents an opportunity to investigate these associations further. Understanding the distribution and role of rs9929218 and rs6983267 among Kurdish individuals affected by CRC could provide valuable insights into the genetic underpinnings of CRC in this population and contribute to the development of tailored screening and prevention strategies. Addressing this gap through diverse, population-based research is crucial for a more comprehensive understanding of CRC susceptibility and risk stratification.

This study aims to assess the prevalence of rs9929218 in the CDH1 gene and rs6983267 in the 8q24 region among Kurdish CRC patients. By elucidating the distribution of these SNPs within a specific ethnic group, we aim to fill the existing research gap and enhance the understanding of CRC genetics. Furthermore, our findings may support the advancement of personalized medicine in oncology, leading to improved outcomes for patients across diverse populations.

2. Methods

2.1. Sample populations

As part of a self-funded project, 290 blood samples were collected from CRC patients at Hiwa Hospital in Sulaymaniyah to investigate the presence of two SNPs. In addition, 100 blood samples were obtained from healthy individuals (54 males and 46 females), aged 37 – 79 years (median age: 59). CRC cases were selected based on the availability of clinicopathological data and the presence of at least 50% tumor tissue in the biopsy specimens and tumor block. The clinicopathological characteristics of the CRC patients are presented in Table 1.

2.2. DNA extraction

DNA was extracted from 0.4 mL of blood collected in EDTA tubes using the QIAamp DNA Blood Kit (Qiagen, Germany), following the manufacturer's protocol. The extracted DNA was eluted in 100 μL of buffer and stored at −20°C until further use.

2.3. Primer design and thermal cycling conditions

For detecting both SNPs in this study, single specific primer (SSP)-polymerase chain reaction (PCR) was employed. For each SNP, two forward primers were designed – one specific for the mutant allele and another for the wild-type allele – along with a common reverse primer. This primer design strategy was applied to both SNPs. The genomic sequences of both SNPs were obtained from the National Center for Biotechnology Information[1]. Primer design was performed using Primer3 software[2]. Primer specificity was evaluated using UCSC *in silico* PCR[3] and MFEprimer-2.0[4] to exclude potential primer-dimer formations. To confirm the results, a subset of samples containing both wild-type and mutant alleles was selected for direct, bidirectional Sanger sequencing. Additional primer sets were used to amplify the SNP regions for sequencing. PCR products

[1] http://www.ncbi.nlm.nih.gov/pubmed/
[2] http://biotools.umassmed.edu/bioapps/primer3_www.cgi
[3] http://genome.ucsc.edu/cgi-bin/hgPcr?command=start
[4] http://biocompute.bmi.ac.cn/CZlab/MFEprimer-2.0/index.cgi/check_dimer

Table 1. The clinicopathological features of CRC patients in the study

Variable	Classification	*n* (%)
Sex	Male	151 (56.5)
	Female	139 (43.5)
Age	Median	69 (43 – 88)
Duke's stage	A	39 (10)
	B	97 (31.7)
	C	126 (43.4)
	D	28 (7.9)
Vascular invasion	V0	149 (47.9)
	V1	101 (31.3)
	V2	40 (10.6)
Nodal stage	N0	57 (51.3)
	N1	150 (34.8)
	N2	83 (13.7)
Tumor stage	T1	48 (16.5)
	T2	37 (12.7)
	T3	138 (47.5)
	T4	67 (23.1)

Abbreviation: CRC: Colorectal cancer.

were purified using the QIAquick PCR Purification Kit (Qiagen, Netherlands) following the manufacturer's protocol. Sequencing was performed directly using the corresponding PCR primers. The resulting chromatograms were analyzed using Chromas Lite software (v2.01, Technelysium Pty Ltd, Australia) and sequence alignment was conducted using the Basic Local Alignment Search Tool (BLAST)[5] to compare the sequences with wild-type reference sequences. All primer sequences are listed in Table 2. The PCR reaction was performed in a final volume of 25 μL, containing 1× HotShot master mix (Cadama Medical, UK), 250 nM of each primer, and 20 ng template DNA. Thermal cycling conditions were as follows: initial denaturation at 95°C for 5 min, followed by 40 cycles of 95°C for 10 s, 55°C for 30 s, and 72°C for 10 s.

2.4. Statistical analysis

All statistical analyses were conducted using SPSS (v.26, IBM Corporation, US). The Hardy-Weinberg equilibrium (HWE) was assessed in the control group using the Chi-square test to determine whether genotype distributions deviated from expected proportions. Associations between rs9929218 in *CDH1* and rs6983267 in 8q24 with CRC risk were evaluated using Chi-square tests and Fisher's exact tests, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated to estimate the strength of associations.

For categorical variables such as sex, tumor grade, TNM stage, perineural invasion, vascular invasion, and tumor location, Chi-square tests were used to compare distributions between wild-type and mutant SNP groups. In cases where expected frequencies in any category were below 5, Fisher's exact test was used as an alternative. Continuous variables, including tumor size and age, were assessed using the Mann–Whitney U-test, as these data did not follow a normal distribution. To adjust for potential confounders, including age, sex, tumor grade, and TNM staging, logistic regression analysis was applied. All statistical tests were two-tailed, and $p<0.05$ was considered statistically significant.

3. Results

3.1. SSP-PCR and genotyping strategy

Genotyping was performed using real-time PCR followed by melt curve analysis, allowing the differentiation between wild-type and mutant alleles based on distinct melting temperatures. Homozygous wild-type and homozygous mutant samples exhibited single melting peaks, while heterozygous samples displayed two distinct peaks representing both alleles (Figures 1 and 2). To validate the accuracy of the PCR-based genotyping approach, a subset of six samples – two homozygous wild-type, two homozygous mutant, and two heterozygous – was selected for Sanger sequencing. The sequencing results were consistent with the initial genotyping, confirming the reliability of the PCR-based approach in detecting these SNPs.

3.2. Association of rs9929218 and rs6983267 SNPs with CRC

Analysis of genotype distributions revealed a higher prevalence of rs9929218 (*CDH1*) and rs6983267 (8q24) among CRC patients compared to healthy controls (Table 3). However, increased prevalence alone does not establish an independent association, even when statistically significant in univariate analyses. To address this, we applied both univariate analysis (Chi-square and Fisher's exact tests) and multivariate logistic regression adjusting for age, sex, tumor grade, and TNM stage. The logistic regression analysis did not confirm either SNP as an independent risk factor for CRC, suggesting that the observed associations may be influenced by other confounding clinicopathological variables.

3.3. Association of SNPs with CRC risk

To determine whether rs9929218 and rs6983267 independently contribute to CRC risk, logistic regression

[5] http://www.ncbi.nlm.nih.gov/blast/bl2seq/wblast2.cgi

Table 2. Primer sequences for wild-type and mutant alleles of the two SNPs

SNPs	Primers (5' to 3')	Target	Location on chromosomes
rs9929218	GTTGTACAGTCATCTGCAAGCACATGTG	Outer forward	Chr16: 68786794
	ATTCAAAGGTTCTGAATTCCACACCG	Wild-type (G)	Chr16: 68787018
	ATTCAAAGGTTCTGAATTCCACACCA	Mutant (A)	Chr16: 68787018
	GGGAGAGAAATTCCAGGGGTAGTTAACA	Outer reverse	Chr16: 68787220
rs6983267	ATTAGAAAACCTGATTTCCCTTCCAGCT	Outer forward	Chr8: 127400871
	GTCCTTTGAGCTCAGCAGATGAAGGG	Wild-type (G)	Chr8: 127401035
	GTCCTTTGAGCTCAGCAGATGAAGGT	Mutant (T)	Chr8: 127401035
	TGTCTGTATACACAGCCCAGTCTAAGGC	Outer Reverse	Chr8: 127401225

Abbreviation: SNP: Single-nucleotide polymorphism.

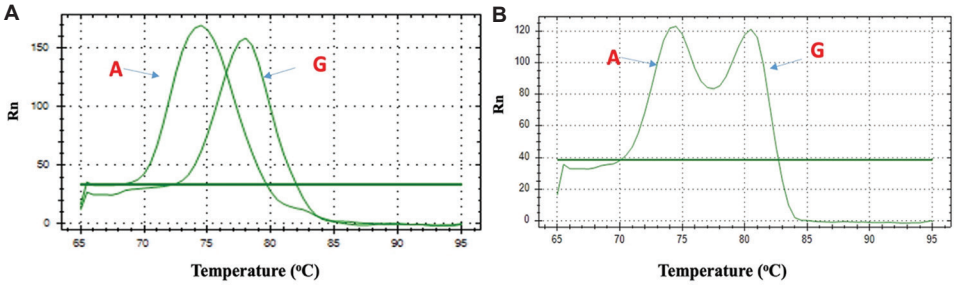

Figure 1. SNP genotyping for rs9929218 in *CDH1* by melt curve analysis using multiplex PCR. (A) Representative melt curve profiles of homozygous samples, where the wild-type allele (G) exhibits a higher melting temperature than the mutant allele (A). (B) Representative melt curve profile of heterozygous samples displaying two distinct peaks, corresponding to the wild-type (G) and mutant (A) alleles. Abbreviations: PCR: Polymerase chain reaction; SNP: Single-nucleotide polymorphism.

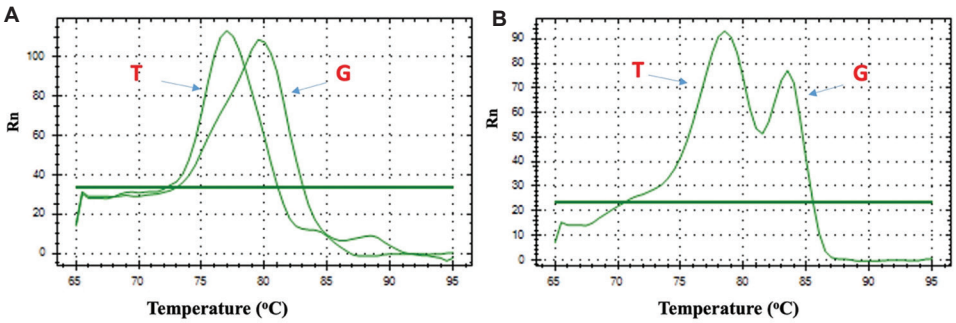

Figure 2. SNP genotyping for rs6983267 in 8q24 by melt curve analysis using multiplex PCR. (A) Representative melt curve profiles of homozygous samples, where the wild-type allele (G) exhibits a higher melting temperature than the mutant allele (T). (B) Representative melt curve profile of heterozygous samples displaying two distinct peaks, corresponding to both the wild-type (G) and mutant (T) alleles. Abbreviations: PCR: Polymerase chain reaction; SNP: Single-nucleotide polymorphism.

analysis was performed, adjusting for age, sex, tumor grade, and TNM staging. After controlling for these confounders, neither rs9929218 (p=0.194) nor rs6983267 (p=0.271) maintained statistical significance in predicting CRC susceptibility (Table 4). These findings suggest that, although these SNPs are more frequent among CRC patients, their role as independent risk factors is not supported when clinical and demographic variables are taken into account. The loss of significance after adjustment indicates that the observed associations may be influenced by tumor-related or genetic confounders.

3.4. Association of SNPs with clinicopathological features

Further analysis explored the relationship between these SNPs and various clinicopathological characteristics. Univariate analysis revealed significant associations between mutations in rs9929218 and rs6983267 and more

Table 3. Association of the two SNPs with CRC

SNP	CRC with SNP (*n*)	CRC without SNP (*n*)	Normal with SNP (*n*)	Normal without SNP (*n*)	*p* (Chi-square test)	*p* (Fisher`s Exact test)
rs9929218 (*CDH1*)	59	231	7	93	0.003	0.001
rs6983267 (8q24)	77	213	11	89	0.002	0.001

Abbreviations: CRC: colorectal cancer; SNP: Single-nucleotide polymorphism.

Table 4. Genotype and allele distributions of the two SNPs in the CRC and control groups

SNP	Genotype/allele	CRC	Control	OR (Crude)	*p* (Crude)	*p* (Logistic regression)
		n (%)	*n* (%)			
rs9929218(CDH1)	GG	231 (79.6)	93 (93)	0.836187	0.192903	0.194
	GA	53 (18.3)	6 (6)	3.115491	**0.003919***	0.194
	AA	6 (2.1)	1 (1)	2.076125	0.685527	0.686
	G	515 (88.7)	192 (96)	0.895557	0.279718	0.279
	A	65 (11.3)	8 (4)	2.876493	**0.002497***	0.279
rs6983267 (8q24)	GG	213 (73.5)	89 (89)	0.802455	0.120263	0.271
	GT	66 (22.7)	10 (10)	2.330108	**0.010653***	0.271
	TT	11 (3.8)	1 (1)	3.817235	0.316886	0.317
	G	492 (84.8)	189 (94)	0.859381	0.144846	0.144
	T	88 (15.2)	12 (6)	2.614609	**0.000944***	0.144

Notes: *$p<0.05$; Bold values indicate statistically significant results at $p<0.05$.
Abbreviations: CRC: colorectal cancer; OR: Odds ratio; PCR: Polymerase chain reaction; SNP: Single-nucleotide polymorphism.

advanced tumor stage (T3 and above) ($p<0.001$). Similarly, nodal involvement was significantly correlated with mutation status ($p=0.001$). In addition, tumors located in the colon were more frequently associated with these mutations compared to rectal tumors ($p=0.006$), suggesting a potential site-specific effect of these polymorphisms.

Multivariate logistic regression analysis, adjusted for age, sex, tumor grade, and TNM stage, confirmed that associations with tumor stage ($p=0.030$), nodal involvement ($p=0.027$), and perineural invasion ($p=0.015$) remained statistically significant. These findings suggesting a potential role of these SNPs in tumor progression, particularly in relation to advanced tumor stage (T3 and T4), rather than overall TNM stage (Table 5).

These results indicate that while rs9929218 and rs6983267 are not independent predictors of overall CRC risk, they may serve as markers of aggressive tumor behavior, particularly with respect to invasion and metastatic potential.

3.5. Genetic association analysis and HWE testing

HWE testing was conducted to evaluate whether genotype distributions deviated from expected proportions (Table 6). In CRC cases, rs9929218 showed significant deviation from HWE ($p=0.0023$), suggesting a potential role in disease susceptibility. However, the control group exhibited only a minor deviation ($p=0.043$), indicating that the variation observed in cases is unlikely to be attributed to population stratification. Similarly, rs6983267 deviated from HWE in CRC cases ($p=0.011$), while control group genotypes were closer to equilibrium ($p=0.048$).

Case-control association analysis further indicated that rs9929218 was significantly associated with CRC ($p=0.022$), whereas rs6983267 did not reach statistical significance ($p=0.090$). Due to the low frequency of homozygous mutant genotypes (AA for rs9929218 and TT for rs6983267), the analysis primarily focused on comparing heterozygotes (GA and GT) with wild-type genotypes (GG) under a dominant genetic model. However, after adjusting for clinical covariates using logistic regression, neither rs9929218 ($p=0.194$) nor rs6983267 ($p=0.271$) remained significant independent predictors of CRC risk (Table 7). Additional analysis of clinical parameters revealed significant associations between CRC progression and tumor size ($p=0.041$), tumor grade ($p=0.034$), TNM staging ($p=0.041$), and Duke stage ($p=0.038$), while vascular invasion was marginally significant ($p=0.050$) and perineural invasion did not reach statistical significance ($p=0.087$) (Table 7). To improve model accuracy, multicollinearity among clinical variables was evaluated using the Variance Inflation Factor (VIF), leading to the removal of highly correlated variables.

Table 5. Comparison of clinic-pathological features between wild-type and mutant SNPs (rs9929218 and rs6983267)

Features	Wild-type SNPs	Mutant SNPs	Test	Test statistics	*p*	*p* (multivariate logistic regression)
Age (years)	67.54% (±2.31)	65.18 (±3.07)	Mann–Whitney U-test	U=4325.5	1.0	0.890
Gender (*n*)						
Male	89	62	Chi-square	χ^2=3.24	0.072	0.112
Female	97	42				
Anatomical sites (*n*)						
Colon	136	90	Chi-square	χ^2=7.46	0.006*	0.049*
Rectum	51	13				
Tumor size (cm)	3.48 (±0.33)	5.87 (±1.06)	Mann–Whitney U	U=277	<0.001*	0.038*
Tumor grade (*n*)						
Low grade	124	50	Chi-square	χ^2=2.76	0.097	0.41
High grade	71	45				
Tumor stage (*n*)						
T2 or earlier	105	34	Chi-square	χ^2=24.55	<0.001*	0.031*
T3 or later	70	81				
Nodal stage (n)						
N0	60	11	Chi-square	χ^2=13.52	0.001*	0.027*
N1	83	30				
N2	63	43				
TNM stage (*n*)						
Stages 1 and 2	52	33	Chi-square	χ^2=0.21	0.644	0.472
Stages 3 and 4	133	72				
Perineural invasion (*n*)						
Absent	151	36	Chi-square	χ^2=45.89	<0.001*	0.015*
Present	42	61				
Vascular invasion (*n*)						
Absent	98	54	Chi-square	χ^2=0.0	1.0	0.785
Present	89	49				

Note: *p<0.05 (two-tailed significance).
Abbreviation: SNP: Single-nucleotide polymorphism.

4. Discussion

CRC is a multifactorial disease influenced by both genetic and environmental factors. Identifying genetic polymorphisms associated with CRC susceptibility is crucial for understanding disease pathogenesis and improving risk stratification. In this study, we investigated the clinical relevance of two SNPs – rs9929218 in *CDH1* and rs6983267 in the 8q24 region – among Kurdish CRC patients in Al-Sulaymaniyah province, Iraq. Our initial univariate analysis suggested a significant association between both SNPs and CRC risk, with rs9929218 detected in 20.34% of CRC cases and 7% of controls (p=0.003), and rs6983267 found in 26.55% of CRC cases and 11% of controls (p=0.002). However, after adjusting for confounding factors such as age, sex, tumor grade, and TNM staging, multivariate logistic regression did not support these associations (rs9929218: p=0.194; rs6983267: p=0.271). These findings suggest that while these SNPs may be more prevalent in CRC patients, their associations with CRC susceptibility may be confounded by other clinical variables.

The rs9929218 polymorphism in *CDH1* has been previously associated with CRC risk, particularly in European populations.[4,7] *CDH1* encodes E-cadherin, a key adhesion protein that regulates epithelial integrity, and its dysregulation is implicated in tumor progression and metastasis.[17,18] Some studies have suggested that rs9929218 may affect E-cadherin expression or function, thereby

Table 6. HWE assessment for rs9929218 and rs6983267 in CRC cases and controls

SNP	Group	Observed genotype frequencies	Expected genotype frequencies	*p*-value
rs9929218	CRC	GG: 231 GA: 53 AA: 6	GG: 228.64 GA: 57.72 AA: 3.64	0.0023
rs9929218	Control	GG: 93 GA: 6 AA: 1	GG: 92.16 GA: 7.68 AA: 0.16	0.043
rs6983267	CRC	GG: 213 GT: 66 TT: 11	GG: 208.68 GT: 74.65 TT: 6.68	0.011
rs6983267	Control	GG: 89 GT: 10 TT: 1	GG: 88.36 GT: 11.28 TT: 0.36	0.048

Notes: Expected genotype frequencies were calculated under HWE using allele frequencies derived from observed genotypes; *p*-values were computed using Fisher's Exact test.
Abbreviations: CRC: colorectal cancer; HWE: Hardy-Weinberg equilibrium; SNP: Single-nucleotide polymorphism.

Table 7. Logistic regression analysis adjusting for clinical variables.

Variable	β	SE	*p*
rs9929218	2.3173	1.783	0.194
rs6983267	−4.4398	4.032	0.271
Age	−0.4991	0.436	0.253
Tumor size	1.283	0.523	0.041
Gender (male vs. female)	0.785	0.289	0.118
Anatomical site (colon vs. rectum)	−0.914	0.421	0.089
Tumor grade (low vs. high)	1.612	0.749	0.034
Tumor stage (T2 and earlier vs. T3 and later)	2.034	0.892	0.041
Nodal invasion (present vs. absent)	−1.211	0.512	0.074
TNM stages (stages 1 and 2 vs. stages 3 and 4)	1.903	0.973	0.050
Perineural invasion (present vs. absent)	0.989	0.654	0.087
Vascular invasion (present vs. absent)	−0.632	0.419	0.102

Abbreviations: β: Regression coefficients; SE: Standard errors; SNP: Single-nucleotide polymorphism.

increasing the risk of colorectal adenomas and invasive carcinoma.[5] Our study identified a higher frequency of the A allele in CRC cases (11.3%) compared to the controls (4%), showing a significant association in the unadjusted analysis (p=0.0025). This aligns with previous research demonstrating a link between rs9929218 and increased CRC risk.[12] However, logistic regression analysis did not confirm an independent effect, suggesting that other clinical or genetic factors may contribute to CRC susceptibility in our population. This finding is consistent with a meta-analysis that reported ethnic differences in the effect size of rs9929218 on CRC risk, with inconsistent findings across diverse populations.[19]

The 8q24 region is known as a "gene desert" but harbors regulatory elements that influence the expression of oncogenes such as *MYC*, a key driver of CRC.[8] The rs6983267 SNP has been linked to an increased risk of CRC in multiple populations, particularly in individuals carrying the T allele.[11,20] Functional studies have shown that rs6983267 enhances transcription factor binding, leading to increased MYC expression and activation of Wnt signaling, both of which are critical in colorectal carcinogenesis.[21] In our study, the T allele was detected in 15.2% of CRC cases compared to 6% of controls (p=0.0009), with the GT genotype showing a higher CRC risk (p=0.0107) in the unadjusted analysis. These findings support previous reports that rs6983267 may play a role in CRC susceptibility.[22] However, as with rs9929218, logistic regression did not confirm an independent association (p=0.271), suggesting that its effect may be modulated by other genetic or environmental factors. This aligns with findings from a large genome-wide association study (GWAS), in which rs6983267 was significantly associated with CRC in unadjusted models but lost significance after accounting for confounders.[23]

Beyond CRC, the rs9929218 polymorphism has been associated with increased susceptibility to other gastrointestinal tumors, including gastric and esophageal cancers, particularly in East Asian populations.[24,25] Similarly, rs6983267 has been linked not only to CRC but also to other solid tumors such as gastric, prostate, and pancreatic cancers.[5] However, GWAS have most consistently confirmed its strong association with CRC, suggesting a tumor-type-specific regulatory role.[26] These findings indicate that while these SNPs are not exclusive to CRC, their prevalence and functional impact may vary across cancer types and populations.

CRC risk is known to vary across ethnic groups, likely due to differences in genetic background, environmental exposures, and dietary patterns.[2] The frequency of rs9929218 and rs6983267 risk alleles in the Kurdish population appears to be comparable to those reported in Middle Eastern populations but differs from European cohorts.[27] For example, a study in an Iranian cohort found a similar association between rs6983267 and CRC risk,[9] while a meta-analysis in European populations reported a higher prevalence of the T allele (up to 20%) compared to our findings (15.2%).[10] These variations highlight the importance of conducting population-specific studies to better understand CRC genetic epidemiology.

Although our study did not confirm an independent effect of rs9929218 or rs6983267 on CRC risk, these SNPs

remain potential biomarkers for genetic screening. Given their association with CRC susceptibility in previous studies, future research should explore larger multi-ethnic cohort studies to confirm whether these SNPs influence CRC risk independently or in combination with other genetic factors.[11] In addition, gene-environment interactions, including dietary patterns and inflammatory markers, may modify genetic risk. Further functional studies are needed to determine how rs9929218 and rs6983267 influence gene expression and CRC pathogenesis.[28] Moreover, integrating these SNPs into polygenic risk scores could improve risk prediction and contribute to personalized medicine.[19]

Our study has several limitations. The relatively small sample size may have reduced statistical power, and the lack of environmental and lifestyle data (e.g., diet, smoking, and physical activity) limits our ability to account for additional risk factors. Furthermore, functional validation was not performed, and future studies should investigate the biological effects of these SNPs on gene expression and tumor behavior. Despite these limitations, our findings provide valuable insights into CRC genetics in an understudied population.

5. Conclusion

This study provides insights into the prevalence and potential clinical significance of rs9929218 in *CDH1* and rs6983267 in the 8q24 region among Kurdish CRC patients. The findings indicate that these SNPs are more frequently detected in CRC cases compared to controls, suggesting a potential role in CRC susceptibility. However, after adjusting for confounding factors such as age, sex, and tumor characteristics, neither SNP remained an independent predictor of CRC risk. Despite this, significant associations were observed between these SNPs and clinicopathological features, particularly advanced tumor stage (T3 and T4) and perineural invasion, which may indicate a role in tumor progression rather than initiation. The study highlights the importance of conducting population-specific genetic research to enhance our understanding of CRC risk in underrepresented groups. Given the study's limitations, including the sample size and the absence of functional validation, further investigations involving larger, well-powered cohorts, and functional assays are needed to confirm these associations and elucidate the biological mechanisms underlying these genetic variants. Future research should also explore how these SNPs interact with environmental and lifestyle factors to refine risk stratification and contribute to personalized screening and prevention strategies for CRC.

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Conflict of interest

The author declares no conflicts of interest.

Author contributions

This is a single-authored article.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Komar University of Science and Technology (Approval number: KUST-SP25-03-01-DEN). Written informed consent was obtained from all participants before sample collection. The study adhered to the ethical principles outlined in the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from all participants for the use or publish their anonymized data in this study.

Availability of data

Data are available from the corresponding author on reasonable request.

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