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Association of *FADS1* (rs174537), *BDNF* (rs6265), and *NPY* (rs16147) Polymorphisms with Colorectal Cancer Risk in a Turkish Population

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Abstract

Background/Objectives: Colorectal cancer (CRC) arises from the interplay between inherited susceptibility and environmental exposures such as diet, yet most genetic association data come from East Asian and European populations. This study examined whether variants in genes that govern fatty acid metabolism (*FADS1* rs174537), neurotrophic signaling (*BDNF* rs6265), and neuropeptide signaling (*NPY* rs16147) are associated with CRC risk in a Turkish population. **Methods**: We genotyped the three variants in 84 patients with CRC and 84 healthy controls (42 men and 42 women in each group) using allele-specific real-time PCR and analyzed them using exact tests, age- and sex-adjusted conventional and Firth logistic regression, and false discovery rate (FDR) correction. **Results**: The *BDNF* and *NPY* variants showed no association with CRC. The *FADS1* genotype distribution differed between groups ($p = 0.005$; FDR $q = 0.030$): GG homozygotes were markedly under-represented among patients (1.6% vs. 17.1%), a pattern that persisted after adjustment for age and sex and in bias-reduced regression, with no evidence of effect modification by sex. However, *FADS1* allele frequencies did not differ, and all three variants showed a marked excess of heterozygotes inconsistent with Hardy–Weinberg equilibrium in both patients and controls, pointing to possible genotyping error. **Conclusions**: Our results do not establish *FADS1* as a protective marker. Instead, they highlight the FADS1–arachidonic acid axis as a candidate pathway for CRC susceptibility that warrants validation with independent genotyping in larger cohorts with dietary and molecular data.

Keywords: colorectal cancer; *FADS1*; *BDNF*; *NPY*; polymorphism; case–control study; Hardy–Weinberg equilibrium; arachidonic acid

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1. Introduction

Colorectal cancer (CRC) remains a significant global public health issue. Current data indicate that CRC is the third most commonly diagnosed malignancy and the second leading cause of cancer-related death [1]. Although CRC incidence has traditionally been higher in developed regions such as North America, Europe, and Australia, it is rising rapidly in many developing and transitional economies, reflecting shifting lifestyles and demographic patterns [2]. Despite significant advances in screening programs, surgical management, and adjuvant therapies, the prognosis for advanced-stage CRC remains poor, with a five-year survival rate of approximately 14% [3]. These observations underscore the need for improved risk stratification and early detection methods that account for both environmental factors and genetic predisposition.

CRC is a multifactorial disorder arising from complex interactions between genetic predisposition and environmental determinants [4]. Environmental and lifestyle risk factors, including dietary habits, physical inactivity, excess body weight, tobacco use, alcohol consumption, and chronic inflammatory conditions such as inflammatory bowel disease, contribute to CRC development [4]. Inherited genetic variation is estimated to account for approximately 35% of CRC susceptibility, underscoring the role of genetic factors in its etiology [5]. Over the past two decades, genome-wide association studies (GWAS) have advanced understanding of CRC's molecular and genetic basis by identifying numerous single-nucleotide polymorphisms (SNPs) associated with disease susceptibility across diverse populations [6]. These variants are located in genes involved in biological pathways critical to CRC development, including cell proliferation, immune response, metabolism, and inflammation [7].

Among these pathways, lipid metabolism and polyunsaturated fatty acid (PUFA) biosynthesis have attracted considerable attention in recent CRC studies. The fatty acid desaturase 1 (*FADS1*) gene encodes delta-5 desaturase, which catalyzes the conversion of dihomo-γ-linolenic acid (DGLA) to arachidonic acid (AA), a key step in long-chain PUFA biosynthesis [8]. AA serves as a precursor for several biologically active lipid mediators, including prostaglandin E_2 (PGE_2), which exerts a substantial influence on inflammation, tumor formation, and CRC development [9,10]. Notably, genetic association studies have identified a significant association between *FADS1* variants, especially rs174537, and CRC risk in East Asians. *FADS1* variants are associated with altered AA formation, leading to altered inflammatory responses in the gastrointestinal microenvironment [8]. FADS1-mediated nutrigenetic interactions suggest that genetic factors affect CRC risk in ways that depend on the dietary habits of different populations [9].

In addition to metabolic pathways, neurotrophic factors and neuropeptides have also been linked to cancer biology. Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, supports neuronal survival, synaptic plasticity, and neural development [11]. Beyond its regulatory role in the nervous system, BDNF contributes to tumor progression by activating the tropomyosin receptor kinase B (TrkB) signaling pathway, which regulates cell proliferation, migration, and survival [12]. The functional *BDNF* Val66Met polymorphism (rs6265) affects BDNF intracellular trafficking and activity-dependent secretion and has been extensively studied in neurological and psychiatric disorders. More recently, BDNF has also been implicated in the pathogenesis of various cancers, including breast, liver, lung, and gastric cancers, as well as chronic diseases, although results remain inconsistent [12,13].

Similarly, neuropeptide Y (NPY), a neurotransmitter peptide that regulates appetite, stress responses, and cardiovascular function, has been linked to tumor biology [14,15]. NPY acts through seven-transmembrane G protein-coupled receptors (Y1–Y5), with the Y1 receptor prominently expressed in CRC tissues. Experimental studies suggest that

NPY signaling can stimulate angiogenesis, enhance tumor cell survival, and promote tumor progression via receptor-mediated mechanisms [15,16]. The rs16147 variant of the *NPY* gene is known to regulate NPY expression and to have functional consequences in metabolic and cardiovascular diseases [14]. However, its potential role in CRC susceptibility remains underexplored.

Previous research has shown that a *FADS1* variant is significantly associated with increased CRC risk, suggesting that lipid metabolism may play a role in CRC development [17]. However, limited information exists on whether this association holds in Mediterranean and Middle Eastern populations [10,18]. Differences in genomic architecture and gene–environment interactions may affect disease susceptibility. In addition, although BDNF and NPY signaling have been implicated in colorectal tumor biology, the contribution of *BDNF* and *NPY* polymorphisms to CRC risk has not been explored. The three variants were selected based on prior genetic and functional evidence. rs174537 was among the genome-wide significant variants at the 11q12.2 (*FADS*) locus identified in the largest East Asian GWAS of CRC [17] and is one of the strongest genetic determinants of FADS1 activity and circulating AA levels [8]; rs6265 (Val66Met) alters activity-dependent BDNF secretion, and rs16147 alters *NPY* expression [14]. We acknowledge that a candidate-gene design cannot capture the polygenic architecture of CRC, which is increasingly investigated through GWAS, polygenic risk scores, and integrated multi-omics approaches [4,5]; rather, the present study aimed to provide population-specific data on biologically motivated variants from an under-represented population. The pathways linking these variants to colorectal carcinogenesis are summarized in Figure 1. This study examined the relationship between the *FADS1* rs174537, *BDNF* rs6265, and *NPY* rs16147 polymorphisms and CRC risk in a Turkish population. Simultaneously investigating three variants involved in metabolic, neurotrophic, and neuropeptide signaling pathways may provide new insights into CRC molecular mechanisms.

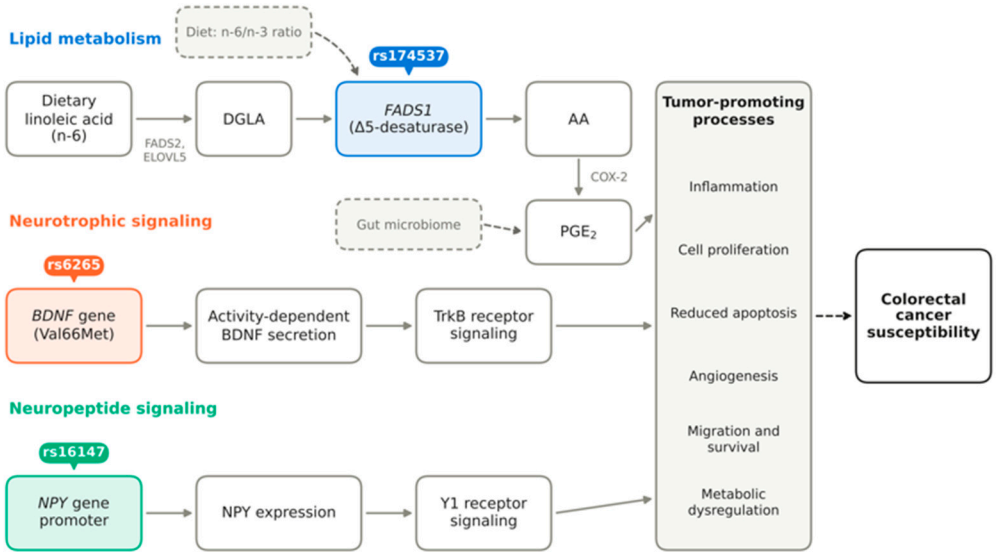


Figure 1. Conceptual framework linking the studied germline polymorphisms to pathways implicated in colorectal carcinogenesis. *FADS1* rs174537 may modulate delta-5 desaturase (Δ5-desaturase) activity and thus the conversion of dihomo-γ-linolenic acid (DGLA) to arachidonic acid (AA), the precursor of prostaglandin E_2 (PGE_2); dietary fatty acids and the gut microbiome act as modifiers (dashed boxes). *BDNF* rs6265 (Val66Met) alters activity-dependent BDNF secretion and TrkB receptor signaling, and *NPY* rs16147 alters *NPY* expression and Y1 receptor signaling. Blue, orange, and green denote the lipid-metabolism, neurotrophic, and neuropeptide pathways, respectively, and the colored labels mark the positions of the studied polymorphisms; gray boxes summarize the downstream tumor-

promoting processes. Solid arrows indicate established biochemical or signaling steps; the dashed arrow to colorectal cancer susceptibility indicates the hypothesized link examined in this study.

2. Materials and Methods

2.1. Study Design and Participants

This case–control study was conducted at the Medical Faculty, Aziz Sancar Institute of Experimental Medicine, and the Institute of Health Sciences, Istanbul University, Istanbul, Türkiye, from January 2020 to December 2023. The study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (Project No.: TDK-2017-25435; approval date: 25 January 2019) and was conducted in accordance with the Declaration of Helsinki. We obtained written informed consent from all participants before enrollment. The case group comprised 84 patients with histologically confirmed colorectal adenocarcinoma diagnosed at the Department of General Surgery. Eligible patients were aged ≥ 18 years and had no history of other malignancies. The control group included 84 healthy individuals recruited from the same geographic region through hospital-based health screening programs. Controls had no history of malignancy, no colorectal adenomas, and no family history of CRC among first-degree relatives. Each group comprised 42 men and 42 women.

2.2. Blood Collection and DNA Extraction

Peripheral venous blood samples (5 mL) were collected from all participants under sterile conditions and placed in commercially available tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. Genomic DNA was extracted from peripheral blood leukocytes using the standard salting-out method. The concentration and purity of the isolated DNA were assessed spectrophotometrically (NanoDrop 2000, Thermo Scientific, Waltham, MA, USA). Samples with an A260/A280 absorbance ratio of 1.8–2.0 were considered of good purity.

2.3. Genotyping Analysis

We genotyped the *FADS1* rs174537, *BDNF* rs6265, and *NPY* rs16147 polymorphisms using allele-specific real-time polymerase chain reaction (PCR) on a CFX96 Touch Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA, USA). We designed allele-specific primers to distinguish wild-type and variant alleles. Primer sequences were as follows: *FADS1* (rs174537), allele-specific primers 5′-GCTCTCCCTCTGTCTTGGACC-3′ and 5′-GCTCTCCCTCTGTCTTGGACG-3′, common primer 5′-GATGGACCCCCAGTTTCTTCT-3′; *BDNF* (rs6265), allele-specific primers 5′-TTGGCTGACACTTTCGAACACG-3′ and 5′-TTGGCTGACACTTTCGAACACA-3′, common primer 5′-TCCTCCAGCAGAAAGAGAAGAGGA-3′; *NPY* (rs16147), allele-specific primers 5′-CCTGCCAACAGGACTACCAA-3′ and 5′-CCTGCCAACAGGACTACCAT-3′, common primer 5′-TCAGCAAACTGGGGGAATAG-3′. PCR amplification was performed under the following conditions: initial denaturation at 95 °C for 3 min; 40 cycles of denaturation at 95 °C for 20 s, primer-specific annealing for 30 s (58 °C for *FADS1*, 60 °C for *BDNF*, and 56 °C for *NPY*), and extension at 72 °C for 30 s; and a final extension at 72 °C for 6 min. We determined genotypes from the cycle threshold (Ct) values of the allele-specific amplification curves, allowing discrimination among wild-type homozygous, heterozygous, and variant homozygous genotypes.

2.4. Statistical Analysis

Statistical analyses were performed on the original individual-level dataset in R (version 4.4.3; supplementary analyses in version 4.3.3) (R Foundation for Statistical Computing, Vienna, Austria); the SPSS data file (IBM SPSS Statistics, version 27.0.1; IBM Corp., Armonk,

NY, USA) was imported with the foreign (version 0.8-87) package. Before analysis, the case–control group variable was cross-checked against an independent case-status variable (no discordant records were found), and missing values were tabulated for age, sex, and each polymorphism by group. Samples without a valid genotype call for a given polymorphism were excluded from the analyses of that polymorphism only (complete-case analysis); therefore, the number of valid observations is reported for each analysis.

Age was presented as mean ± standard deviation (SD) and as median (range) and compared between groups using Welch's *t*-test and the Wilcoxon rank-sum test. Sex distribution was compared between groups using Pearson's χ^2 test. We calculated genotype frequencies by direct counting and derived allele counts from the genotypes. Because several genotype cells had low expected counts, the overall 2 × 3 genotype distributions were compared using Fisher's exact test, with Pearson's χ^2 test reported for reference. Allelic associations were evaluated using Fisher's exact test on 2 × 2 allele tables; odds ratios (ORs) were calculated as conditional maximum-likelihood estimates with exact 95% confidence intervals (CIs). The same approach was used for the dominant model (carriers of the second listed allele vs. homozygotes for the first listed allele) and the recessive model (homozygotes for the second listed allele vs. the other two genotypes). The first listed (reference) alleles were G for *BDNF* rs6265, T for *FADS1* rs174537, and A for *NPY* rs16147.

Deviation from Hardy–Weinberg equilibrium (HWE) in the control group was assessed using an exact test [19]; HWE was also examined in the patient group. To estimate associations independent of age and sex, multivariable logistic regression models with CRC status as the outcome and age (continuous) and sex as covariates were fitted for each polymorphism, with genotype coded either as a three-level factor (codominant model; reference: homozygotes for the first listed allele) or as an additive allele dosage (0, 1, or 2 copies of the second listed allele). ORs with Wald 95% CIs are reported. To account for multiple testing, the Benjamini–Hochberg false discovery rate (FDR) procedure [20] was applied jointly to the six primary tests (three overall genotype tests and three allelic tests), and FDR-adjusted q values are reported. Because some genotype categories contained very few individuals, all adjusted models were also fitted using Firth's bias-reduced penalized-likelihood logistic regression [21,22], with profile penalized-likelihood 95% CIs and penalized likelihood-ratio tests. Effect modification by sex was assessed by adding a genotype (additive) × sex interaction term and comparing nested models with a likelihood-ratio test. Genotype and allele distributions were compared between patients and controls separately in men and women using Fisher's exact test. Genotype contrasts and regression models were considered secondary and exploratory analyses. As a sensitivity analysis, unadjusted logistic regression models were fitted to the same complete-case samples and compared with the adjusted models. All tests were two-sided, and $p < 0.05$ was considered statistically significant. An SPSS syntax file reproducing the core analyses was also prepared.

3. Results

3.1. Study Population and Data Quality

This study included 168 participants: 84 patients with CRC and 84 healthy controls. We found no discordance between the group and case-status variables, and age and sex data were complete for all participants. The mean age was 47.14 ± 11.86 years in patients with CRC and 49.13 ± 11.65 years in the controls; the difference was not statistically significant (Welch's *t*-test, $p = 0.275$; Wilcoxon rank-sum test, $p = 0.227$; Table 1). Each group included 42 men and 42 women (50.0%), and the sex distribution did not differ between groups ($p = 1.000$; Table 1). Valid genotype calls were obtained for 155 participants for *BDNF* rs6265 (13 missing), 140 for *FADS1* rs174537 (28 missing), and 157 for *NPY* rs16147 (11 missing).

Missing *FADS1* genotypes were more frequent among patients (20/84, 23.8%) than among the controls (8/84, 9.5%).

Table 1. Demographic characteristics and genotyping completeness of patients with colorectal cancer and the controls.

Characteristic	Control (n = 84)	Cancer (n = 84)	p Value
Age (years)			
Mean ± SD	49.13 ± 11.65	47.14 ± 11.86	0.275 [a]
Median (range)	49.00 (22–79)	47.50 (23–77)	0.227 [b]
Sex, n (%)			
Male	42 (50.0)	42 (50.0)	1.000 [c]
Female	42 (50.0)	42 (50.0)	
Valid genotype calls, n (%)			
BDNF rs6265	77 (91.7)	78 (92.9)	—
FADS1 rs174537	76 (90.5)	64 (76.2)	—
NPY rs16147	77 (91.7)	80 (95.2)	—

[a] Welch's t-test. [b] Wilcoxon rank-sum test. [c] Pearson's χ^2 test. Percentages of valid genotype calls are calculated relative to all participants in each group. SD, standard deviation. n, number of participants; p, probability value.

Genotype distributions in the control group deviated significantly from HWE for all three polymorphisms (exact test, all $p < 0.001$; Section 3.5). In each case, this deviation reflected a marked excess of heterozygotes: the observed heterozygote proportions in the controls were 93.5% for *BDNF*, 78.9% for *FADS1*, and 84.4% for *NPY* compared with approximately 50% expected under HWE. The results of the association analyses presented below should therefore be interpreted in light of this finding.

3.2. Genetic Analysis of the BDNF Polymorphism

Table 2 presents the genotype and allele distributions for the *BDNF* rs6265 polymorphism. The heterozygous GA genotype was the most common in both groups. The frequencies of the GG, GA, and AA genotypes were 5.1%, 89.7%, and 5.1% in patients with CRC and 3.9%, 93.5%, and 2.6% in controls, respectively. The genotype distribution did not differ significantly between the groups (Fisher's exact test, $p = 0.755$; FDR $q = 1.000$).

Table 2. Genotype and allele distributions of the *BDNF* rs6265 polymorphism in patients with colorectal cancer and the controls.

Comparison	Control n (%)	Cancer n (%)	p Value	OR (95% CI)
Genotype distribution				
GG	3 (3.9)	4 (5.1)	0.755	—
GA	72 (93.5)	70 (89.7)		
AA	2 (2.6)	4 (5.1)		
Allele distribution				
G allele	78 (50.6)	78 (50.0)	0.910	Reference
A allele	76 (49.4)	78 (50.0)		1.026 (0.642–1.642)
Genetic models				
Dominant: GA + AA vs. GG	74 (96.1)/3 (3.9)	74 (94.9)/4 (5.1)	1.000	0.751 (0.106–4.609)
Recessive: AA vs. GG + GA	2 (2.6)/75 (97.4)	4 (5.1)/74 (94.9)	0.681	2.018 (0.280–22.946)

Data are presented as n (%) among participants with a valid genotype call. p-values were obtained using Fisher's exact test (2 × 3 for the genotype distribution; 2 × 2 for alleles and genetic models). ORs (conditional maximum-likelihood estimates with exact 95% CIs) express the odds of colorectal cancer (patients relative to controls). For alleles, the OR refers to the second listed allele, with the first listed allele as the reference. For genetic models, values are given as n (%) for the first listed genotype group/n (%) for the comparison group. OR, odds ratio; CI, confidence interval. Valid genotypes: controls, $n = 77$; patients, $n = 78$.

The A allele frequency was 50.0% in patients with CRC and 49.4% in the controls (A vs. G: OR = 1.026, 95% CI: 0.642–1.642; $p = 0.910$). Neither the dominant model (GA + AA vs. GG: OR = 0.751, 95% CI: 0.106–4.609; $p = 1.000$) nor the recessive model (AA vs. GG + GA: OR = 2.018, 95% CI: 0.280–22.946; $p = 0.681$) showed a significant association.

3.3. Genetic Analysis of the FADS1 Polymorphism

Table 3 presents results for the *FADS1* rs174537 polymorphism. In patients with CRC, the TT, GT, and GG genotype frequencies were 7.8%, 90.6%, and 1.6%, respectively, compared with 3.9%, 78.9%, and 17.1%, respectively, in controls. The overall genotype distribution differed significantly between the groups (Fisher's exact test, $p = 0.005$; Pearson's $\chi^2 = 9.864$, $p = 0.007$), and this difference remained significant after FDR correction ($q = 0.030$). The difference was driven primarily by the GG genotype, which was observed in only one patient but in 13 controls (recessive model, GG vs. TT + GT: OR = 0.078, 95% CI: 0.002–0.548; $p = 0.003$). The dominant model was not significant (GT + GG vs. TT: OR = 0.487, 95% CI: 0.073–2.623; $p = 0.469$).

Table 3. Genotype and allele distributions of the *FADS1* rs174537 polymorphism in patients with colorectal cancer and the controls.

Comparison	Control *n* (%)	Cancer *n* (%)	*p* Value	OR (95% CI)
		Genotype distribution		
TT	3 (3.9)	5 (7.8)	0.005	—
GT	60 (78.9)	58 (90.6)		
GG	13 (17.1)	1 (1.6)		
		Allele distribution		
T allele	66 (43.4)	68 (53.1)	0.119	Reference
G allele	86 (56.6)	60 (46.9)		0.678 (0.411–1.116)
		Genetic models		
Dominant: GT + GG vs. TT	73 (96.1)/3 (3.9)	59 (92.2)/5 (7.8)	0.469	0.487 (0.073–2.623)
Recessive: GG vs. TT + GT	13 (17.1)/63 (82.9)	1 (1.6)/63 (98.4)	0.003	0.078 (0.002–0.548)

Data are presented as *n* (%) among participants with a valid genotype call. *p*-values were obtained using Fisher's exact test (2 × 3 for the genotype distribution; 2 × 2 for alleles and genetic models). ORs (conditional maximum-likelihood estimates with exact 95% CIs) express the odds of colorectal cancer (patients relative to controls). For alleles, the OR refers to the second listed allele, with the first listed allele as the reference. For genetic models, values are given as *n* (%) for the first listed genotype group/*n* (%) for the comparison group. OR, odds ratio; CI, confidence interval. Valid genotypes: controls, $n = 76$; patients, $n = 64$.

In contrast, the allelic analysis showed no significant association. The G allele frequency was 46.9% in patients with CRC and 56.6% in the controls (G vs. T: OR = 0.678, 95% CI: 0.411–1.116; $p = 0.119$; FDR $q = 0.299$).

3.4. Genetic Analysis of the NPY Polymorphism

Table 4 presents the genotype and allele distributions for the *NPY* rs16147 polymorphism. The AG genotype was the most common in both groups. The frequencies of the AA, AG, and GG genotypes were 3.8%, 93.8%, and 2.5% in patients with CRC, and 7.8%, 84.4%, and 7.8% in controls, respectively. The genotype distribution did not differ significantly between the groups (Fisher's exact test, $p = 0.150$; FDR $q = 0.299$).

Table 4. Genotype and allele distributions of the *NPY* rs16147 polymorphism in patients with colorectal cancer and the controls.

Comparison	Control *n* (%)	Cancer *n* (%)	*p* Value	OR (95% CI)
		Genotype distribution		
AA	6 (7.8)	3 (3.8)	0.150	—
AG	65 (84.4)	75 (93.8)		
GG	6 (7.8)	2 (2.5)		
		Allele distribution		
A allele	77 (50.0)	81 (50.6)	1.000	Reference
G allele	77 (50.0)	79 (49.4)		0.975 (0.612–1.555)
		Genetic models		
Dominant: AG + GG vs. AA	71 (92.2)/6 (7.8)	77 (96.3)/3 (3.8)	0.322	2.159 (0.441–13.837)
Recessive: GG vs. AA + AG	6 (7.8)/71 (92.2)	2 (2.5)/78 (97.5)	0.162	0.306 (0.029–1.780)

Data are presented as *n* (%) among participants with a valid genotype call. *p*-values were obtained using Fisher's exact test (2 × 3 for the genotype distribution; 2 × 2 for alleles and genetic models). ORs (conditional maximum-likelihood estimates with exact 95% CIs) express the odds of colorectal cancer (patients relative to controls). For alleles, the OR refers to the second listed allele, with the first listed allele as the reference. For genetic models, values are given as *n* (%) for the first listed genotype group/*n* (%) for the comparison group. OR, odds ratio; CI, confidence interval. Valid genotypes: controls, $n = 77$; patients, $n = 80$.

The G allele frequency was 49.4% in patients with CRC and 50.0% in controls (G vs. A: OR = 0.975, 95% CI: 0.612–1.555; $p = 1.000$). Neither the dominant model (AG + GG vs. AA: OR = 2.159, 95% CI: 0.441–13.837; $p = 0.322$) nor the recessive model (GG vs. AA + AG: OR = 0.306, 95% CI: 0.029–1.780; $p = 0.162$) showed a significant association.

3.5. Hardy–Weinberg Equilibrium in the Control Group

Table 5 summarizes the HWE assessment in the control group. For all three polymorphisms, observed heterozygosity substantially exceeded the heterozygosity expected from the allele frequencies, and the deviation from HWE was statistically significant (exact test, $p < 0.001$ for all three polymorphisms). A similar excess of heterozygotes was observed in the patient group (observed heterozygosity: *BDNF*, 89.7%; *FADS1*, 90.6%; *NPY*, 93.8%; exact test, all $p < 0.001$), indicating that the deviation affected both groups. Figure 2 shows the genotype distributions in patients and controls, along with the genotype frequencies expected in controls under HWE.

Table 5. Hardy–Weinberg equilibrium of the studied polymorphisms in the control group.

Polymorphism	*n*	Genotype Counts	Obs. *H*	Exp. *H*	Exact HWE *p*
BDNF rs6265	77	GG 3/GA 72/AA 2	0.935	0.500	<0.001
FADS1 rs174537	76	TT 3/GT 60/GG 13	0.789	0.491	<0.001
NPY rs16147	77	AA 6/AG 65/GG 6	0.844	0.500	<0.001

Obs. *H*, observed proportion of heterozygotes; Exp. *H*, heterozygosity expected under HWE ($2pq$), calculated from the control allele frequencies (frequency of the second listed allele: *BDNF* A, 0.494; *FADS1* G, 0.566; *NPY* G, 0.500). HWE, Hardy–Weinberg equilibrium. *n*, number of controls with a valid genotype call.

3.6. Covariate-Adjusted Logistic Regression, Sensitivity Analyses, and Multiple-Testing Correction

Table 6 presents results from logistic regression models adjusted for age and sex. Neither age nor sex was significantly associated with CRC status in any model (all $p > 0.05$). For *FADS1* rs174537, the GG genotype was associated with lower odds of CRC than the TT genotype (OR = 0.041, 95% CI: 0.003–0.509; $p = 0.013$), whereas the GT genotype was not (OR = 0.576, 95% CI: 0.127–2.615; $p = 0.475$). In the additive model, each additional G allele was associated with lower odds of CRC (OR = 0.213, 95% CI: 0.071–0.640; $p = 0.006$).

These estimates were nearly identical to those from models adjusted for age only (GG vs. TT: OR = 0.040, 95% CI: 0.003–0.489; per G allele: OR = 0.212, 95% CI: 0.071–0.636). Firth's bias-reduced regression yielded attenuated but consistent estimates (GG vs. TT: OR = 0.065, 95% CI: 0.005–0.476; $p = 0.006$; per G allele: OR = 0.239, 95% CI: 0.074–0.622; $p = 0.002$; Figure 3 and Supplementary Table S1). No significant associations were observed for *BDNF* rs6265 or *NPY* rs16147 in any model. In the unadjusted sensitivity analysis, the smallest genotype-term p values were 0.015 for *FADS1*, 0.686 for *BDNF*, and 0.250 for *NPY*, consistent with the adjusted models. No participants were excluded because of missing covariate data.

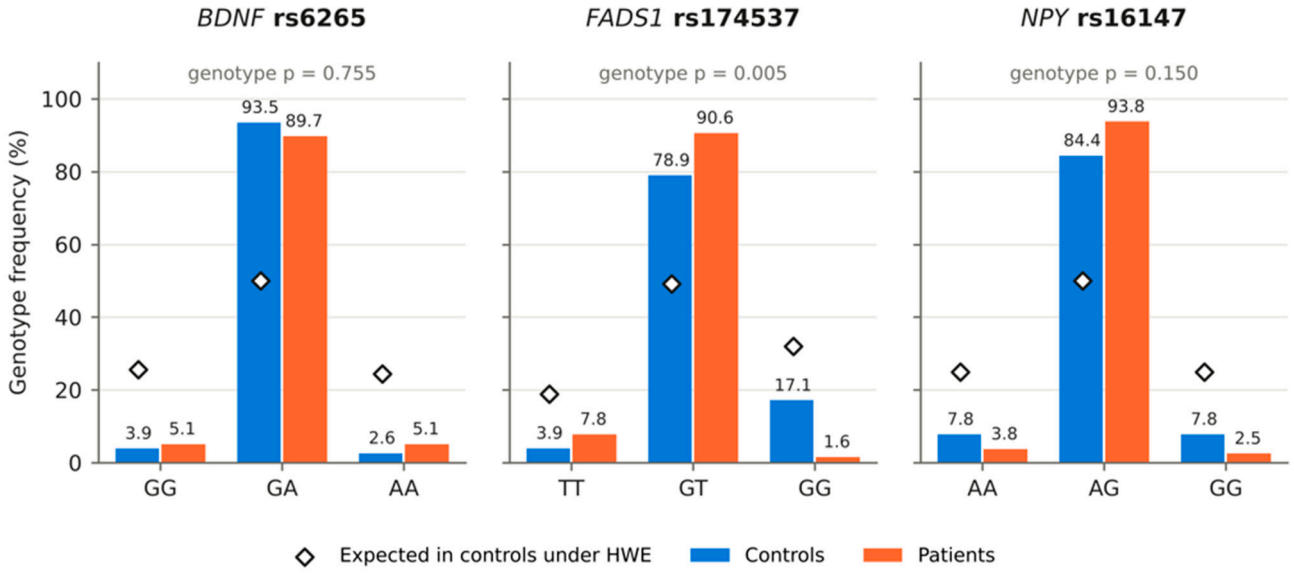


Figure 2. Genotype distributions of *BDNF* rs6265, *FADS1* rs174537, and *NPY* rs16147 in controls (blue) and patients with colorectal cancer (orange). Bars show observed genotype frequencies among participants with a valid genotype call, with percentages above the bars. Open diamonds show the genotype frequencies expected in controls under Hardy–Weinberg equilibrium (HWE), calculated from control allele frequencies; the excess of heterozygotes relative to these expected values corresponds to the HWE deviation reported in Table 5. Genotype p-values were obtained using Fisher's exact test (2 × 3).

Table 6. Logistic regression analysis of the association between the studied polymorphisms and colorectal cancer, adjusted for age and sex.

Polymorphism/Model	Term	*n*	OR (95% CI)	*p* Value
		BDNF rs6265		
Codominant	GA vs. GG	155	0.842 (0.178–3.992)	0.828
	AA vs. GG		1.661 (0.167–16.504)	0.665
	Age (per year)		0.984 (0.957–1.012)	0.271
	Female vs. male		1.157 (0.606–2.210)	0.658
Additive	Per A allele	155	1.239 (0.408–3.758)	0.705
	Age (per year)		0.983 (0.956–1.011)	0.223
	Female vs. male		1.154 (0.605–2.203)	0.664
		FADS1 rs174537		
Codominant	GT vs. TT	140	0.576 (0.127–2.615)	0.475
	GG vs. TT		0.041 (0.003–0.509)	0.013
	Age (per year)		0.973 (0.943–1.004)	0.086
	Female vs. male		1.351 (0.661–2.760)	0.409
Additive	Per G allele	140	0.213 (0.071–0.640)	0.006
	Age (per year)		0.973 (0.943–1.004)	0.086
	Female vs. male		1.259 (0.623–2.545)	0.521

Table 6. *Cont.*

Polymorphism/Model	Term	*n*	OR (95% CI)	*p* Value
		NPY rs16147		
Codominant	AG vs. AA	157	2.474 (0.582–10.517)	0.220
	GG vs. AA		0.649 (0.076–5.526)	0.692
	Age (per year)		0.978 (0.951–1.007)	0.135
	Female vs. male		1.135 (0.594–2.168)	0.702
Additive	Per G allele	157	0.884 (0.336–2.322)	0.802
	Age (per year)		0.981 (0.954–1.009)	0.175
	Female vs. male		1.055 (0.559–1.990)	0.869

Each polymorphism was analyzed in a separate model including genotype, age (continuous), and sex. ORs express the odds of colorectal cancer and are presented with Wald 95% CIs. In the codominant model, genotype was entered as a three-level factor with homozygotes for the first listed allele as the reference; in the additive model, genotype was entered as the number of copies of the second listed allele (0, 1, or 2). Estimates from Firth's bias-reduced regression are shown in Figure 3 and Supplementary Table S1. OR, odds ratio; CI, confidence interval. *n*, number of participants with a valid genotype call.

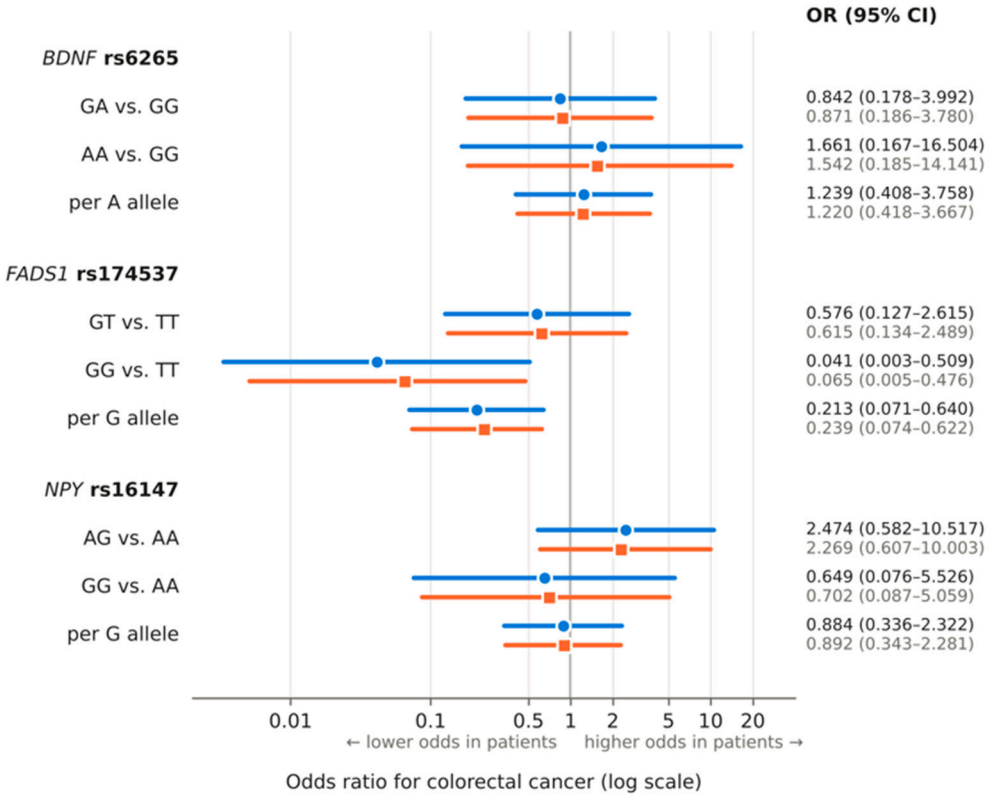


Figure 3. Odds ratios for colorectal cancer by genotype, adjusted for age and sex. Circles and blue lines show conventional logistic regression estimates with Wald 95% confidence intervals (CIs); squares and orange lines show Firth's bias-reduced regression estimates with profile penalized-likelihood 95% CIs. Reference genotypes: GG (*BDNF* rs6265), TT (*FADS1* rs174537), and AA (*NPY* rs16147); allele effects refer to each additional copy of the second listed allele. The *x*-axis is on a logarithmic scale; the vertical line marks an odds ratio of 1.

Sex-stratified analyses are presented in Supplementary Table S2. For *BDNF* rs6265 and *NPY* rs16147, genotype and allele distributions did not differ between patients and controls in either men or women (all $p > 0.2$). For *FADS1* rs174537, the GG genotype was less frequent among patients in both sexes (men: 3.2% vs. 12.5%; women: 0.0% vs. 22.2%); the overall genotype difference was significant in women ($p = 0.008$) but not in men ($p = 0.138$), and allele frequencies did not differ in either sex. The genotype × sex interaction was not significant for any polymorphism (*BDNF*, $p = 0.870$; *FADS1*, $p = 0.623$;

NPY, $p = 0.519$), indicating no evidence that the associations differ by sex. Given the small sex-specific subgroups, these results should be interpreted with caution.

After Benjamini–Hochberg correction across the six primary tests, only the overall *FADS1* genotype comparison remained significant ($q = 0.030$); the overall genotype comparisons for *BDNF* ($q = 1.000$) and *NPY* ($q = 0.299$), as well as the allelic comparisons for *BDNF* ($q = 1.000$), *FADS1* ($q = 0.299$), and *NPY* ($q = 1.000$), were not significant.

4. Discussion

Genetic polymorphisms are common variations in the DNA sequence that can influence gene expression, protein function, and biological processes involved in disease development. In complex diseases such as CRC, these polymorphisms may affect metabolic, inflammatory, and cellular signaling pathways that contribute to disease development; identifying polymorphisms associated with CRC risk can therefore provide insights into risk factors and disease mechanisms [17]. This case–control study investigated the association between the *FADS1* rs174537, *BDNF* rs6265, and *NPY* rs16147 polymorphisms and CRC susceptibility in a Turkish population. The main findings were that *BDNF* rs6265 and *NPY* rs16147 were not associated with CRC at the genotype, allele, or genetic-model level. In contrast, the overall *FADS1* rs174537 genotype distribution differed between patients and controls. This *FADS1* difference survived FDR correction and adjustment for age and sex, but it was not accompanied by a difference in allele frequencies and occurred amid marked HWE deviation.

The most important observation for interpreting these results is the pronounced excess of heterozygotes in the control group across all three polymorphisms (78.9–93.5% vs. approximately 50% expected). An excess of this magnitude, occurring simultaneously at three unlinked loci in a population-based sample, is unlikely to have a biological explanation. Population stratification and inbreeding typically produce a deficit rather than an excess of heterozygotes, and selection would not be expected to act in the same direction on three unrelated variants in healthy controls. The most plausible explanation is systematic genotype misclassification, for example, nonspecific amplification by the mismatched allele-specific primer in the real-time PCR assay, which would cause true homozygotes to be called heterozygotes; sample handling or data transfer errors cannot be excluded either. Because HWE testing in controls is a standard quality-control step in genetic association studies [19], these deviations substantially limit the reliability of all genotype-based estimates reported here. Moreover, the same pattern was present in patients (observed heterozygosity 89.7–93.8%), indicating that the problem affected both groups.

This consideration applies particularly to the *FADS1* finding. The significant overall genotype difference and the recessive and covariate-adjusted associations all depend on the GG homozygote category, which included only one patient and 13 controls. This is precisely the category most likely to be affected if homozygotes were systematically misclassified as heterozygotes, and the small cell counts are reflected in the very wide CIs (e.g., 0.003–0.509 for GG vs. TT). Firth's bias-reduced regression, which reduces small-sample bias arising from such sparse cells, attenuated but did not eliminate the association (GG vs. TT: OR = 0.065, 95% CI: 0.005–0.476); however, no statistical method can correct genotype misclassification. In addition, missing *FADS1* genotypes were considerably more frequent among patients than among the controls (23.8% vs. 9.5%); if genotyping failure was related to genotype, this could have introduced differential bias. The absence of a significant difference in allele frequencies (OR = 0.678, 95% CI: 0.411–1.116) further indicates that the genotype-level signal is not robust. For these reasons, we regard the *FADS1* finding as hypothesis-generating rather than as evidence of a protective or risk effect. In particular, these data should not be interpreted as evidence of genetic protection against CRC.

With these caveats, an association between *FADS1* variation and CRC would be biologically plausible. Variants in the *FADS* gene cluster have been linked to CRC susceptibility in GWAS [5,17], and rs174537 influences PUFA metabolism; its genotypes are associated with AA levels [23]. AA is a precursor of several pro-inflammatory mediators, including PGE_2, which is involved in tumor formation and progression [9,10]. Experimental studies have confirmed that increased AA metabolism and PGE_2 signaling can promote colorectal tumorigenesis by stimulating cell proliferation, inhibiting apoptosis, and promoting angiogenesis [24]; Xu et al. showed that FADS1 overactivity enhances AA metabolism and promotes tumor growth through increased PGE_2 synthesis and altered intestinal microbiome composition [24]. Genetic variation affecting *FADS1* may therefore alter endogenous AA production and inflammatory signaling within the colorectal microenvironment. Notably, the rs174537 G allele has been associated with higher circulating AA concentrations [25]; under this mechanistic model, a lower frequency of GG homozygotes among patients would be directionally unexpected, adding another reason to interpret the present result with caution.

Another important aspect of FADS1-mediated CRC risk is the potential gene–diet interaction. The fatty acid composition of the diet, particularly the omega-6/omega-3 fatty acid ratio, has been shown to influence inflammatory responses and CRC risk [26]. Because FADS1 converts dietary fatty acids into biologically active lipid mediators and because *FADS1* variants, particularly rs174537, are strongly associated with circulating PUFA levels, including AA [25], individuals with different *FADS1* genotypes may differ in their metabolic responses to dietary fatty acid intake. Dietary intake data were unavailable in the present study, so we could not evaluate these interactions.

Several studies have examined the relationship between the *BDNF* rs6265 (Val66Met) polymorphism and cancer, suggesting that this variant may be involved in cancer-related processes. However, its effects appear to vary across cancer types [27,28]. BDNF overexpression in CRC tumor tissue may contribute to CRC progression via the BDNF–TrkB signaling pathway [12,13]; however, to the best of our knowledge, the association between the *BDNF* rs6265 polymorphism and CRC risk has not been previously studied. The Val66Met polymorphism is associated with alterations in activity-dependent BDNF secretion rather than baseline expression levels. In the present study, we observed no association between *BDNF* rs6265 and CRC in any analysis.

The *NPY* rs16147 polymorphism is a functional variant in the *NPY* promoter; previous studies show that it affects *NPY* expression and is linked to various metabolic phenotypes, including obesity, insulin resistance, metabolic syndrome, and dietary effects on adiposity and blood pressure [29]. Because metabolic dysregulation, including altered lipid metabolism and inflammatory processes, plays a critical role in colorectal carcinogenesis [30,31], *NPY* rs16147 may plausibly influence CRC risk. Although NPY signaling has been implicated in cancer-related processes [32], cancer-specific association studies of this polymorphism are scarce, and our study found no significant association between *NPY* rs16147 and CRC.

Our findings should also be considered in the context of large-scale genomic studies. GWAS and multi-omic analyses of more than 100,000 CRC cases have identified numerous common susceptibility loci [4,5]. Among the variants studied here, only the *FADS* region has GWAS support: rs174537 was among the genome-wide significant variants at the 11q12.2 locus in the largest East Asian GWAS [17], and common *FADS*-cluster variants act as cis-expression quantitative trait loci (eQTLs) for *FADS1* in multiple tissues in the Genotype-Tissue Expression (GTEx) project [33], providing a plausible regulatory mechanism. In contrast, to our knowledge, *BDNF* rs6265 and *NPY* rs16147 have not been reported as CRC susceptibility loci in GWAS, which is consistent with our null findings for these variants. Each GWAS-identified variant confers only a small increase in risk, and clinically useful risk

stratification requires combining many such variants into polygenic risk scores alongside non-genetic risk factors [4,5]. Accordingly, three candidate SNPs, even if validated, could not support personalized risk prediction on their own; our study should be viewed as a contribution of population-specific data to future meta-analyses rather than as a source of clinically applicable biomarkers.

To place these findings in a biological context, Figure 1 summarizes a conceptual framework linking the germline variants under study to colorectal carcinogenesis. In this framework, *FADS1* rs174537 modulates delta-5 desaturase activity and thus the conversion of DGLA to AA, which can be metabolized to PGE_2 and other eicosanoids that promote inflammation, proliferation, and angiogenesis and that interact with dietary fatty acid intake and the gut microbiome [9,10,24]; rs6265 alters activity-dependent BDNF secretion and thereby BDNF–TrkB signaling, which supports tumor cell proliferation and survival [12,13]; and rs16147 alters *NPY* expression and Y1 receptor-mediated signaling, which has been linked to angiogenesis and metabolic regulation [15,16,29]. These hypothesized mechanisms must be distinguished from clinically validated biomarkers: none of the three variants is currently used in CRC risk assessment, and the framework is intended to generate testable hypotheses. Future studies could test it by integrating germline genotypes with tumor transcriptomics, lipidomics, circulating inflammatory markers, gut microbiome profiles, and established molecular features of CRC, such as microsatellite instability status and consensus molecular subtypes. The molecular steps at which each variant is expected to act, including each variant's position within its gene, are illustrated in more detail in Figure 4.

Several limitations should be considered when interpreting these results. First, and most importantly, genotype distributions in the control group deviated markedly from HWE for all three polymorphisms due to an excess of heterozygotes, suggesting possible genotyping error (present in both patients and controls); we did not validate the genotype calls with an independent method (e.g., TaqMan assays or Sanger sequencing) or perform blinded duplicate genotyping. Second, the sample size was small, and the homozygote categories contained very few individuals, resulting in wide CIs and limited power to detect modest effects. Third, genotype data were missing for 6.5–16.7% of participants, depending on the polymorphism, and missingness for *FADS1* was higher among patients than among controls. Fourth, age and sex were the only covariates available for adjustment; information on body mass index, smoking, alcohol consumption, dietary fatty acid intake, and other environmental exposures was unavailable, precluding adjustment for these factors and the evaluation of gene–environment interactions. Fifth, although the overall *FADS1* genotype comparison remained significant after FDR correction, the genetic-model contrasts and regression analyses were exploratory and were not corrected for multiple testing. Sixth, the sex-stratified analyses were based on small subgroups and had limited power. Seventh, tumor tissue was not available; therefore, the relationship between the studied germline polymorphisms and somatic driver mutations such as *TP53*, *APC*, and *KRAS*, microsatellite instability status, or consensus molecular subtypes could not be investigated. Finally, controls were recruited through hospital-based screening programs in a single region, which may limit generalizability.

Further studies are needed before drawing conclusions about *FADS1* rs174537 and CRC risk. As a first step, re-genotyping the current samples, or at least a random subset, using an independent, validated method would clarify whether the observed excess of heterozygotes reflects assay error. Confirmation in larger, independent, ethnically diverse cohorts with HWE-consistent genotype data is also required. Combining genetic analyses with dietary assessments, circulating fatty acid measurements, microbiome studies, and tumor molecular profiling (including *TP53*, *APC*, and *KRAS* mutations, microsatellite insta-

bility, and consensus molecular subtypes) may further elucidate how fatty acid metabolism contributes to CRC.

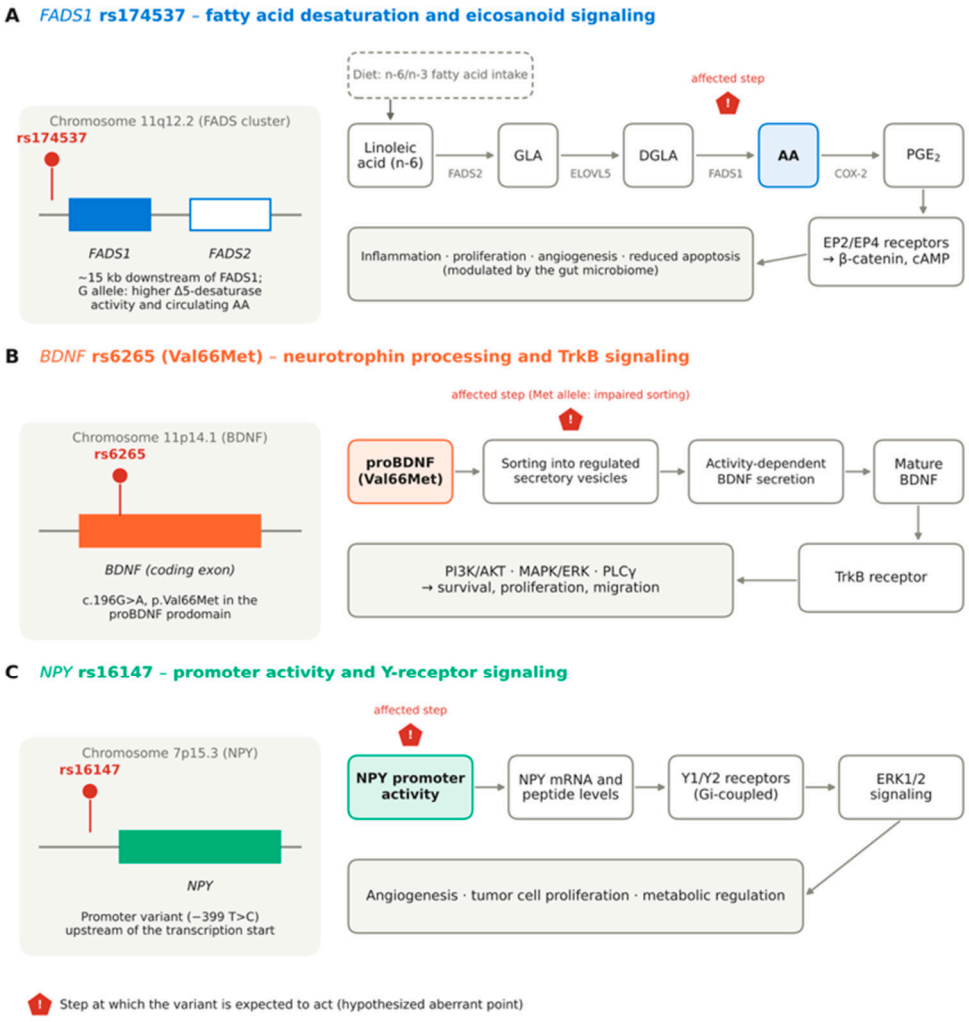


Figure 4. Proposed molecular mechanisms of the studied polymorphisms. (**A**) *FADS1* rs174537 lies approximately 15 kb downstream of *FADS1* in the 11q12.2 *FADS* cluster; its G allele has been associated with higher delta-5 desaturase activity and higher circulating arachidonic acid (AA), the substrate used by cyclooxygenase-2 (COX-2) to produce prostaglandin E_2 (PGE_2), which signals through EP2/EP4 receptors. (**B**) *BDNF* rs6265 (c.196G>A, p.Val66Met) lies in the proBDNF prodomain; the Met allele impairs the sorting of BDNF into the regulated secretory pathway and reduces activity-dependent secretion, thereby affecting TrkB receptor signaling. (**C**) *NPY* rs16147 (−399 T>C) lies in the *NPY* promoter and alters *NPY* expression and downstream Y-receptor signaling. Blue, orange, and green denote the *FADS1*, *BDNF*, and *NPY* pathways, respectively; in each gene track, the red circle marks the position of the variant; dashed boxes indicate modifiers, and gray boxes summarize the downstream cellular effects. Red markers indicate the steps at which each variant is expected to act; these are hypothesized mechanisms that were not tested directly in this study. GLA, γ-linolenic acid; DGLA, dihomo-γ-linolenic acid; ELOVL5, elongation of very-long-chain fatty acids protein 5; PI3K, phosphoinositide 3-kinase; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; PLCγ, phospholipase C-γ.

5. Conclusions

In this Turkish case–control study, *BDNF* rs6265 and *NPY* rs16147 were not associated with CRC susceptibility. The overall *FADS1* rs174537 genotype distribution differed between patients and controls, primarily because the GG genotype was less frequent among patients. This difference persisted after adjustment for age and sex, in bias-reduced regression, and

after FDR correction. However, allele frequencies did not differ, and all three polymorphisms showed marked deviations from HWE in both patients and controls, suggesting possible genotyping error. The *FADS1* finding should therefore be considered hypothesis-generating and requires confirmation with independently validated genotyping in larger cohorts. These three variants alone cannot support personalized CRC risk prediction.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/dna6040061/s1, Table S1: Firth's bias-reduced logistic regression analysis of the association between the studied polymorphisms and colorectal cancer, adjusted for age and sex; Table S2: Sex-stratified genotype and allele distributions of the studied polymorphisms in patients with colorectal cancer and controls.

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Institutional Review Board Statement: This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (Date: 25 January 2019; No.: TDK-2017-25435).

Informed Consent Statement: Written informed consent was obtained from all individual participants in the study. This article does not contain any data that could identify individual participants.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available because they consist of individual-level human genetic information and are subject to privacy restrictions. The R script and SPSS syntax used for the statistical analyses are available from the corresponding author on request.

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Abbreviations

The following abbreviations are used in this manuscript:

AA	Arachidonic acid
BDNF	Brain-derived neurotrophic factor
BH	Benjamini–Hochberg
CI	Confidence interval
COX-2	Cyclooxygenase-2
CRC	Colorectal cancer
Ct	Cycle threshold
DGLA	Dihomo-γ-linolenic acid

EDTA	Ethylenediaminetetraacetic acid
eQTL	Expression quantitative trait locus
FADS1	Fatty acid desaturase 1
FDR	False discovery rate
GTEx	Genotype-Tissue Expression
GWAS	Genome-wide association study
HWE	Hardy–Weinberg equilibrium
NPY	Neuropeptide Y
OR	Odds ratio
PCR	Polymerase chain reaction
PGE_2	Prostaglandin E_2
PUFA	Polyunsaturated fatty acid
SD	Standard deviation
SNP	Single-nucleotide polymorphism
TrkB	Tropomyosin receptor kinase B

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