Published in final edited form as:
Int J Cancer. 2009 May 1; 124(9): 2148–2151. doi:10.1002/ijc.24079.

Dopamine D_2 Receptor Polymorphisms and Adenoma Recurrence in the Polyp Prevention Trial

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Abstract

Epidemiological evidence suggests that obesity may be causally associated with colorectal cancer. Dopamine and the dopaminergic reward pathway have been implicated in drug and alcohol addiction as well as obesity. Polymorphisms within the D2 dopamine receptor gene (*DRD2*) have been shown to be associated with colorectal cancer risk.

We investigated the association between DRD2 genotype at these loci and the risk of colorectal adenoma recurrence in the Polyp Prevention Trial. Odds ratios (OR) and 95% confidence intervals (CI) for risk of adenoma recurrence were calculated using unconditional logistic regression. Individuals with any, multiple (≥2) or advanced adenoma recurrence after 4 years were compared to those without adenoma recurrence. Variation in intake of certain dietary components according to DRD2 genotype at 3 loci (rs1799732; rs6277; rs1800497) was also investigated.

The DRD2 rs1799732 CT genotype was significantly associated with all adenoma recurrence (OR: 1.30; 95% CI: 1.01, 1.69). The rs1800497 TT genotype was also associated with a significantly increased risk of advanced adenoma recurrence (OR: 2.40; 95% CI: 1.11, 5.20).

The rs1799732 CT and rs1800497 TT genotypes were significantly associated with adenoma recurrence in the Polyp Prevention Trial. Increased risk of adenoma recurrence as conferred by DRD2 genotypes may be related to difference in alcohol and fat intake across genotypes.

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Conflict of interest: None

Introduction

Epidemiological evidence associating obesity with colorectal cancer is now deemed 'convincing'1. This association is thought to relate to obesity as a state of chronic low-grade inflammation and/or insulin resistance. Complex neuronal circuitry may modulate food intake. Dopamine modulates motivation and reward pathways in the brain and it has been suggested that dopamine deficiency in obese individuals may perpetuate pathological eating as a means to compensate for decreased activation of these circuits2. Furthermore, dopamine receptors have been identified in the pancreas and the gastrointestinal tract, also a site of significant dopamine production3–5.

A number of single nucleotide polymorphisms (SNPs) in the gene encoding the dopamine D2 receptor (DRD2) have been described. Three SNPs: rs1799732 (also known as DRD2 -141C>del), rs6277 (also known as DRD2 C957T) and rs1800497 (also known as DRD2 "TaqIA") are thought to affect function and expression of the protein6–8 and have been associated with disorders such as Parkinson's disease and schizophrenia, as well as addiction to smoking and alcohol. These 3 SNPs have also been associated with colorectal cancer risk, with a maximum odds ratio (OR) of 2.28 (95% confidence interval (CI): 1.38, 3.76) associated with the rare allele of the rs1799732 SNP9.

We hypothesize that the DRD2 polymorphisms: rs1799732; rs6277; rs1800497, which have been associated with colorectal cancer, may be similarly associated with colorectal adenoma recurrence in the Polyp Prevention Trial (PPT). Furthermore, we will investigate whether intake of certain dietary components might vary across the genotypes at each of the 3 loci.

Subjects and Methods

Study Population

Participants in this study were from the PPT, a large multi-center study randomized control trial to evaluate the effects of a high-fiber, high-fruit and vegetable, low-fat diet on the recurrence of colorectal adenomas. Men and women, aged 35 years or older, with at least one histologically confirmed adenoma removed in the prior 6 months, were randomized to the dietary intervention or control group for 4 years. In order to be eligible potential participants must not have had prior surgically resected adenomatous polyps, or diagnoses with colorectal cancer, inflammatory bowel disease, or a polyposis syndrome. Furthermore, participants were required to have no medical conditions or dietary restrictions that would limit their compliance to the protocol and be ≤150% of their recommended weight and could not be currently using lipid-lowering medications.

A total of 2,079 participants were enrolled in the trial; 1,037 were randomized to the intervention diet and 1,042 assigned to their usual diet. 1,905 participants (91.6%) completed the study, 958 in the intervention group and 947 in the control group.

PPT participants underwent a clearing colonoscopy approximately a year after enrollment to remove potential missed lesions at qualifying examinations and had end-of-trial colonoscopy 4 years after randomization. A detailed description of the study design, dietary intervention, study population, and end-point assessment is reported elsewhere10,11. Participants completed an interviewer-administrated questionnaire, which included demographic, clinical, dietary, supplementation and medication use information at baseline and at each of the four annual follow-up visits. A modified food frequency questionnaire (FFQ) eliciting information on the frequency and portion size of food consumed over the past 12 months12,13 was also completed at each of these visits. Body mass index (BMI) was computed based on measured weight and height at the baseline interview and categorized as

normal (<24.9), overweight (25.0–29.9), and obese (>30.0)14. Recurrence outcomes were defined at year 4 colonoscopy as: any, advanced (≥10 millimeters, or with villous histology or high-grade or severe dysplasia) or multiple (≥2) adenoma recurrence (no adenoma recurrence as referent group).

The study was approved by the institutional review boards of the National Cancer Institute and those of the collaborating centers. All subjects provided written informed consent.

Genotyping

Of the 1,905 participants who completed the PPT, 1,723 (90.4%) of the participants, 673 (89.3%) cases and 1,050 (91.2%) controls, had DNA samples available for genotyping. Genotyping was performed by BioServe Biotechnologies, Ltd. (Laurel, MD). A detailed description of the protocol for this analysis was previously reported15. Briefly, BioServe Biotechnologies, Ltd., used a two-step PCR process (Masscode™, Qiagen Genomics, Bothel, WA) as described by Kokoris *et al.*, 200016, using both touchdown PCR and an identical locus specific PCR. Allele-specific PCR products were polled, subjected to photolysis and analyzed by mass spectrometry. Datagen™ (Qiagen Genomics, Bothel, WA) software was used to call the SNP alleles (manually or automatically). Concordance rate for the (10%) duplicate samples was 99%.

Statistical Analysis

Due to the small number (n = 43) of participants identifying themselves as ‘other’ under the race category, the analysis listed here is limited to those participants identifying themselves as African American or Caucasian.

Unconditional logistic regression was used to estimate the odds ratio (OR; adjusted for age, gender, race, smoking, alcohol, BMI and total fat intake) and 95% CI for the association between genotype (or allele carriage) and risk of adenoma recurrence at year 4 using SAS software (version 8.1, SAS Institute, Cary, NC). ANOVA and χ^2 squared analysis were employed to investigate possible differences in baseline or year 1 (clearing colonoscopy) subject characteristics or dietary variables across DRD2 genotypes at each locus.

Results

Demographic and lifestyle characteristics for the PPT participants with genotyping data are presented in Table 1. A total of 673 (39%) participants had adenoma recurrence at year 4 (at least one adenoma), 1,050 (61%) participants had no adenoma recurrence. Participants with any recurrence were found to be older, to be male and less likely to report regular non-steroidal anti-inflammatory drug (NSAID) use (Table 1).

The DRD2 genotypes were then assessed for possible influence on ‘any’, multiple and advanced adenoma recurrence (at year 4; Table 2). The odds of any adenoma recurrence was significantly increased for individuals with the CT genotype for rs179932 (OR: 1.30, 95% CI: 1.01, 1.69). Individuals with the rs1800497 TT genotype were found to have a significantly increased risk of advanced adenoma recurrence (OR: 2.40; 95% CI: 1.11, 5.20).

Further investigation of DRD2 haplotypes constructed from the rs1799732, rs6277 and rs1800497 SNPs did not add any explanatory power; therefore, only the results of the genotype associations are presented.

A comparison of baseline characteristics across each genotype and locus revealed statistically significant differences in fat intake (as a percentage of total caloric intake)

across DRD2 rs1799732 and rs6277 genotypes (Table 3). In addition, alcohol intake varied across DRD2 rs6277 genotype (Table 3).

Discussion

The DRD2 rs1799732 heterozygote was significantly associated with any adenoma recurrence and the rs1800497 TT genotype was associated with advanced adenoma recurrence in the PPT. Interestingly, we also note that alcohol intake and total fat intake vary significantly across DRD2 rs1799732 and rs6277 genotypes.

Gemignani *et al.*9, previously reported an elevated risk of colorectal cancer for the same three SNPs within DRD2. We have replicated a number of these associations for colorectal adenoma recurrence. The association between rs1800497 and advanced adenoma recurrence should be replicated in a larger study because of the small number of participants with advanced adenoma recurrence within the PPT. The DRD2 rs1799732 SNP comprises of a C deletion in the 5′ untranslated region of DRD2 and is considered a functional polymorphism having been associated with a reduction in basal levels of receptor expression17, though this observation was not replicated in later studies by Ritchie *et al.*8. The rs6277 SNP is a T>C transition at position 957 and codes for the silent change (proline to proline) at codon 319. Duan *et al.*,6 found this change to be associated with alterations of mRNA folding, mRNA stability, and translation of the protein. Lastly the rs1800497 SNP has been associated with a reduction DRD2 receptor density in vivo18.

Possible mechanisms whereby DRD2 receptor polymorphisms might increase risk of CRC were outlined by Gemignani *et al.*, who cited previous references describing progressive reduction on dopamine and dopamine receptor levels within the colon with advancing colon cancer leading to a reduction in intracellular cyclic AMP, an inhibitor of cell growth19. Rubí *et al.*›5 have since described expression of dopamine receptors in the pancreatic beta cells and report that dopamine inhibited glucose-induced insulin secretion, possibly via DRD2. It is likely that DRD2 polymorphisms modulate risk of colorectal adenoma and CRC through complex pathways involving modulation of cell growth (via cyclic AMP) and glucose homeostasis (by modulating insulin release).

The dopaminergic system and DRD2, in particular, has long been implicated in the reward mechanisms in the brain. Specifically, variance in the gene encoding DRD2 has been associated with addictive and compulsive behavior including substance abuse, smoking and obesity20. As with the Gemignani study we found no association between BMI and genotype and minor differences in dietary fat intake by DRD2 rs1799732 and rs6277 genotypes. We did observe some difference in alcohol intake by DRD2 rs6277 genotype. It is worth remarking that PPT participants were, by nature of the study exclusion criteria, ‘healthy’ with atypically low alcohol intake (7.4 g/day in the intervention group; 8.0 g/day in the control group) low prevalence of smoking (13.4%: intervention group; 13.2%: control group) and only borderline overweight in terms of BMI (27.6 kg/m^2 in the intervention group; 27.5 kg/m^2 in the control group). It could be possible that in a population with a higher BMI and/or higher alcohol intake the differences we observed might be of even greater significance21⁻23.

In conclusion, we observed that rs1799732 and rs6277 genotypes were significantly associated with adenoma recurrence in the PPT and that alcohol intake and total fat intake vary significantly across DRD2 rs1799732 and rs6277 genotypes.

Acknowledgments

Funding: This study was funded by the Intramural Research Program, National Cancer Institute, NIH, Bethesda, MD.; Dr Murphy is supported by the Ireland-Northern Ireland-National Cancer Institute Cancer Consortium and the Health Research Board of Ireland.

Abbreviations

BMI	body mass index
CI	confidence interval
DRD2	dopamine D2 receptor
FFQ	Food Frequency Questionnaire
NSAID	non-steroidal anti-inflammatory drug
OR	Odds ratio
PPT	Polyp Prevention Trial
SNP	single nucleotide polymorphism

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Int J Cancer. Author manuscript; available in PMC 2010 May 1.

Table 1

Baseline characteristics of participants in the Polyp Prevention Trial with genotype data by adenoma recurrence

Baseline Characteristic	All subjects *n*=1723	No recurrence *n*=1050	Any recurrence *n*=673	Multiple recurrence *n*=286	Advanced recurrence *n*=109
Age (y)	61.0 ± 10.0	59.8 ± 10.2	62.9 ± 9.3*	64.8 ± 9.3*	65.6 ± 9.2*
Body Mass Index (kg/m^2)	27.6 ± 3.9	27.5 ± 3.9	27.7 ± 3.9	27.9 ± 3.8*	28.0 ± 4.2
Gender (%)					
Male	1,103 (64.2)	624 (59.6)	479 (71.4)*	215 (75.4)*	76 (69.7)
Female	615 (35.8)	423 (40.4)	192 (28.6)	70 (24.6)	33 (30.3)
Race (%)					
White	1,540 (89.6)	938 (89.6)	602 (89.7)	264 (92.6)	98 (89.9)
African American	135 (7.9)	84 (8.0)	51 (7.6)	16 (5.6)	11 (10.1)
Other	43 (2.5)	25 (2.4)	18 (2.7)	5 (1.8)	0
Education (%)					
< High school	425 (24.7)	252 (24.1)	173 (25.8)	79 (27.7)	29 (26.6)
> High school	1,293 (75.3)	795 (75.9)	498 (74.2)	206 (72.3)	80 (73.4)
Smoking status (%)					
Never	683 (39.8)	428 (40.9)	255 (38.0)	111 (38.9)	42 (38.5)
Former	814 (47.4)	489 (46.7)	325 (48.4)	134 (47.0)	55 (50.5)
Current	221 (12.9)	130 (12.4)	91 (13.6)	40 (14.0)†	12 (11.0)
Family history (%)					
No	472 (27.5)	283 (27.0)	189 (28.2)	87 (30.5)	78 (71.6)
Yes	1,246 (72.5)	764 (73.0)	482 (71.8)	198 (69.5)†	31 (28.4)
Regular NSAID use (%)‡					
No	603 (50.8)	380 (48.7)	253 (54.1)	108 (56.3)	45 (58.4)
Yes	582 (49.2)	367 (51.3)	215 (45.9)	84 (43.7)	32 (41.6)

Results are presented as mean ± SD for continuous variables and as percentages for categorical variables. P values were determined by t tests and or χ^2 tests, as appropriate.

*Comparison group: no adenoma recurrence; P < 0.01.

†Comparison group: no adenoma recurrence; P < 0.05.

‡Regular NSAID use includes current use of NSAIDs on a regular basis (>1 per month) reported at three or more yearly study visits. The reference group of no NSAID use includes individuals who reported no current use of NSAIDs on a regular basis (<1 per month) at all five study visits.

Table 2

Genotyped frequency in the Polyp Prevention Trial cohort (excluding those self-selecting as 'other' race: n=43; n=1680) and association with adenoma recurrence, multiple adenoma recurrence and advanced adenoma recurrence at year 4.

Genotype	Frequency	%	Any adenoma recurrence		Multiple adenoma recurrence		Advanced adenoma recurrence	
			n (%)	† OR (95% CI)	n (%)	† OR (95% CI)	n (%)	† OR (95% CI)
DRD2 rs179932 (-141C ins/del)								
CC	1199	76.7	454 (73.6)	*Reference*	201 (76.7)	*Reference*	70 (70.7)	*Reference*
CT	348	21.5	151 (24.5)	***1.30 (1.01,1.69)***	54 (20.6)	1.11 (0.77, 1.59)	27 (27.3)	1.54 (0.93, 2.57)
TT	31	1.8	12 (1.9)	1.25 (0.57, 2.75)	7 (2.7)	2.10 (0.78, 5.62)	2 (2.0)	1.30 (0.27, 6.19)
CT & TT *vs*. CC				**1.30 (1.01, 1.68)**		1.16 (0.81, 1.65)		1.53 (0.92, 2.53)
DRD2_9 rs6277 (957T>C)								
CC	422	25.9	166 (26.2)	*Reference*	67 (24.6)	*Reference*	35 (33.3)	*Reference*
CT	778	48.4	308 (48.6)	1.00 (0.77, 1.29)	137 (50.4)	1.05 (0.74, 1.50)	45 (42.9)	0.68 (0.41, 1.12)
TT	425	25.7	160 (25.5)	0.94 (0.69, 1.26)	68 (25.0)	0.92 (0.61, 1.38)	25 (23.8)	0.66 (0.37, 1.18)
CT & TT *vs*. CC				0.98 (0.77, 1.25)		1.01 (0.72, 1.41)		0.67 (0.42, 1.07)
DRD2_11 rs1800497 (TaqIA)								
CC	1061	64.4	413 (65.6)	*Reference*	180 (66.9)	*Reference*	64 (60.4)	*Reference*
CT	480	31.3	190 (30.2)	1.00 (0.80, 1.26)	76 (28.3)	0.93 (0.68, 1.27)	32 (30.2)	1.09 (0.69, 1.72)
TT	68	4.3	27 (4.3)	0.98 (0.59, 1.65)	13 (4.8)	1.08 (0.55, 2.12)	10 (9.4)	**2.40 (1.11, 5.20)**
CT & TT *vs*. CC				1.00 (0.81, 1.24)		0.95 (0.70, 1.28)		1.25 (0.82, 1.91)

†OR (95% CI) adjusted for age, gender, race, smoking, alcohol, total fat intake and BMI.

Table 3

Selected characteristics of the Polyp Prevention Trial participants by DRD2 genotype.

Baseline Characteristic	DRD2 -141>C rs1799732			DRD2_09 rs6277			DRD2_11 rs1800497†		
	CC	CT	TT	CC	CT	TT	CC	CT	TT
N (%)	1199 (76.0)	348 (22.1)	31 (1.9)	422 (25.9)	778 (47.9)	425 (26.2)	1061 (65.9)	480 (29.8)	68 (4.3)
Family history: n (%)*	335 (27.9)	91 (26.2)	10 (32.3)	96 (22.8)	228 (29.3)	113 (26.6)	294 (27.7)	129 (26.9)	15 (22.1)
BMI: kg/m^2									
< 25	312 (26.0)	84 (24.1)	9 (29.0)	100 (23.7)	212 (27.3)	102 (24.0)	278 (26.2)	119 (24.8)	12 (17.7)
25 – 29	571 (47.6)	176 (50.6)	9 (29.0)	197 (46.7)	367 (47.2)	220 (51.8)	521 (49.1)	214 (44.6)	37 (54.4)
≥ 30	316 (26.4)	88 (25.3)	13 (42.0)	125 (29.6)	199 (25.6)	103 (24.2)	262 (24.7)	147 (30.6)	19 (27.9)
Smoking status: n (%)									
Current	147 (12.3)	53 (15.2)	2 (6.5)	59 (14.0)	100 (12.9)	51 (12.0)	136 (12.8)	64 (13.3)	9 (13.2)
Former	565 (47.1)	160 (46.0)	17 (54.8)	208 (49.3)	369 (47.4)	188 (44.2)	495 (46.7)	234 (48.8)	30 (44.1)
Dietary intake: mean (SD)									
Total folate: mcg/day	422.9 (262.27)	422.7 (311.95)	335.7 (207.32)	410.9 (237.22)	420.2 (283.31)	434.0 (280.42).	420.5 (267.96)	418.3 (265.24)	422.0 (319.02)
Total fiber: g/day	18.4 (8.16)	18.0 (7.58)	16.3 (7.18)	18.0 (8.45)	18.2 (7.84)	18.5 (7.80)	18.3 (7.92)	18.3 (8.03)	18.1 (8.17)
Fat: Total % caloric intake	35.5 (7.32)	35.4 (7.30)	38.4 (8.32)[a]	36.3 (7.46)	35.2 (7.20)[b]	35.34 (7.51)	35.4 (7.31)	35.7 (7.41)	36.2 (7.33)
Alcohol intake: n (%)									
Non-drinkers	493 (74.4)	151 (22.8)	19 (2.9)	197[c] (28.6)	311 (45.2)	180 (26.2)	448 (65.8)	204 (30.0)	29 (4.3)
≤ 7 servings/wk	485 (77.4)	133 (21.2)	9 (1.4)	165 (25.9)	304 (47.7)	180 (26.4)	420 (65.9)	191 (30.0)	26 (4.1)
> 7 servings/wk	221 (76.7)	64 (22.2)	3 (1.0)	60 (20.0)	163 (54.3)	77 (25.7)	193 (66.3)	85 (29.2)	13 (4.47)

[a] Fat intake: CC *v* TT: P=0.03;

[b] Fat intake: CT *v* CC: P=0.02.

[c] DRD2_09 rs6277 by alcohol intake: χ^2=9.68, P=0.05.

* Family history baseline – year 4.

† DRD2_11 rs1800497 is also known as 'TaqIA'. % may not sum to 100 due to rounding and may not sum to n=1680 due to missing data.