Interaction of *DRD2/ANKK1 Taq1A* Genotype with in-Store Retail Food Environment Exposures on Diet Quality in a Cohort of Quebec Adults

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Keywords

Gene-environment interaction · Retail food environment · Diet quality · Population study · Marketing · Dopamine receptor · Differential susceptibility

Abstract

Background/Aims: Gene-environment interactions may be relevant for nutrition outcomes. This study assessed the interaction between *DRD2/ANKK1 Taq1A* genotype and exposures to in-store retail food environment on diet quality. **Methods:** CARTaGENE biobank data ($n = 3,532$) were linked to provincial food retail data. The Canadian adaptation of the Healthy Eating Index 2010 (HEI-C) was calculated from food frequency questionnaires. Generalized linear models adjusted for sociodemographic factors, anthropometrics, and energy intake were used to assess interactions between the *Taq1A* variant and retail food measures. **Results:** A significant inverse interaction was observed between *Taq1A* and ice cream store displays on HEI-C score (estimate: -15.46 [95% confidence interval (CI): $-24.83, -6.10$], $p = 0.0012$) where, among allele carriers, increasing exposure to ice cream displays was associated with a lower HEI-C score as

compared to allele carriers with a lower exposure. A significant positive interaction between *Taq1A* and price of vegetables was also observed, where, among allele carriers, increasing exposure to a higher price was associated with a higher HEI-C score compared to allele carriers with exposure to a lower price (estimate: 2.46 [95% CI: $0.78, 4.14$], $p = 0.0041$). The opposite pattern was observed among non-carriers. **Conclusions:** *DRD2/ANKK1 Taq1A* is associated with adaptive responses to ice cream displays and vegetable prices, suggesting a differential susceptibility to retail environment food cues.

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Background

Diet quality is increasingly recognized as an important modifiable risk factor for cardiometabolic diseases [1]. Both environmental and genetic factors have been associated with human eating behaviour [2], yet the interaction between genetics and the neighbourhood retail food environment on diet quality has not been explored. The retail food environment, including proximity to food retail-

ers and exposure to food marketing, influences eating decisions [3, 4]; however, inter-individual variability may modify responses to food cues in the retail food environment [5, 6]. It is widely acknowledged that genes interact with environment to influence health outcomes, and given the obesogenic nature of the food supply in North America, an investigation of the interaction between gene variants and the retail food environment on dietary outcomes, such as diet quality, would provide insight into novel avenues for prevention of cardiometabolic diseases.

The overall available evidence suggests a role of the retail food environment in influencing cardiometabolic outcomes [3], as significant associations have been reported between increased proximity to unhealthy food retailers and poorer dietary outcomes as well as increased anthropometric risk factors (waist circumference and body mass index [BMI]) [7–13] and prevalence of cardiovascular diseases [14–16]. Despite this supportive evidence, a number of studies have reported null findings with cardiometabolic risk and outcomes [17–20]. The mixed nature of evidence appears to be consistent across different countries [21], despite differences in food environments (e.g., higher prevalence of food deserts in the USA than Canada). While it is possible that the variety of food options available in the retail food environment enables opportunities for both healthy and unhealthy food choices, there has been a lack of consideration of how individuals differ in their behavioural responses to retail food environment exposures.

An intriguing notion that has recently begun to be considered in nutrition research is neurobehavioural genetic differential susceptibility to environmental exposures. Stemming from developmental biology, the differential susceptibility hypothesis proposed by Belsky has been linked with obesogenic behaviours in teens [22] and cognitive and emotional defects in children [23]. The hypothesis suggests that individuals display adaptive responses to both positive and negative environments based on gene-environment interactions [24]. The candidate genes that have been implicated in the hypothesis are related to brain systems that modulate the interplay between environmental exposures and individual adaptive behaviour. They are proposed to function as plasticity genes, reinforcing carriers' responses to both positive and negative environments in a "for better and for worse manner" of responsivity. Thus, an individual may perform poorly in an adverse environment, but in a supportive environment that same individual would adapt to perform well and to a superior extent than non-carriers of the relevant gene variant. The strongest gene candidates

implicated in neurobehavioural differential susceptibility exert effects on brain pathways involved in the reward system and behavioural traits such as impulsivity [22, 23], and include *DRD4* (7-repeat allele), *5-HTTLPR*, *DRD2/ANKK1* (*Taq1A*), *DAT1* (10-repeat allele), and *MAOA* (2-repeat/3-repeat alleles). The majority of these variants are variable number tandem repeats, where a variable number of nucleotides are repeated in a region of DNA. Although common in the population, these particular gene variants have been underexplored in large-scale genomics studies that utilize genome-wide genotyping approaches which measure single nucleotide polymorphisms (SNPs). An exception is the *DRD2/ANKK1 Taq1A* variant (rs1800497), which is a SNP and available on several genome-wide genotyping assays. While historically referred to as a variant in the dopamine D2 receptor (*DRD2*) gene, the SNP is actually located in the adjacent Ankyrin repeat and kinase domain containing 1 (*ANKK1*) gene, about 10 kb downstream from the *DRD2* gene [25]. Individuals who carry 1 or 2 copies of the *Taq1A* allele (referred to as *Taq1A* carriers) have a reduced number of dopamine binding sites in the brain [26], making them less sensitive to the activation of dopamine-based reward circuitry and rendering them more likely to develop addictive behaviours. Indeed, previous research has implicated this variant in substance use and smoking [27], eating behaviour [28], and body weight [29]. Although *DRD2/ANKK1 Taq1A* is a candidate gene for differential susceptibility, its role in influencing dietary outcomes according to environmental exposures has not been explored. Therefore, the objective of this investigation was to evaluate the interaction between *DRD2/ANKK1 Taq1A* genotype and in-store retail food environment exposures on diet quality. We hypothesized that *Taq1A* carriers would display differential patterns of diet quality according to in-store exposures in the retail food environment.

Methods

Study Population

We utilized existing data from the CARTaGENE biobank (<http://www.cartagene.qc.ca/>), a Quebec population cohort study comprised of 40,000 adults aged 40–69 years old from 4 regions of the province: Sherbrooke, Saguenay, Quebec City, and the Greater Montreal Area [30]. The study population is broadly representative of middle-aged adults in the province of Quebec, with the exception that study participants tended to be more highly educated [30], and was designed to assess the stage of life at which adults are particularly vulnerable to the onset of cardiometabolic diseases. Comprehensive medical, lifestyle, residential and measured anthropometric data were collected between 2008 and 2013 and included dietary assessment by food frequency questionnaire (FFQ)

Table 1. Measures of the retail food environment available for investigation

	Variable	Description
Product	Variety	Number of distinct SKUs at point of purchase
Price	Regular price	Regular price is defined as the highest price over 3-month moving windows of each SKU; the weighted average (weights are market shares) of regular prices of all SKUs is then taken within a category to arrive at category price per serving
	Price promotion	Number of weeks in which the price of SKU was at least 2 standard deviations below its average price; data is further aggregated to category level
Promotion (non-price)	In-store display	Percentage of SKUs that are on display at a given time in a category within a community

for the entire study population in 2012. The Canadian adaptation of the Diet History Questionnaire (DHQ) was the dietary assessment tool that was used. The DHQ is a semi-quantitative FFQ comprised of 164 food and beverage items that assesses dietary intake over the previous 12 months, thus providing an estimate of usual dietary intake. Information on both frequency of intake and serving size is obtained. DNA was obtained from blood samples, and genome-wide genotyping was performed on a subset of CARTaGENE participants ($n = 12,073$). The present analysis was approved by CARTaGENE's Sample and Data Access Committee (SDAC), and ethics approval for the present investigation was obtained from the McGill University Faculty of Agriculture and Environmental Sciences Research Ethics Board.

Measures of Retail Food Environment

Traditional measures of the food environment have relied on residential proximity measures to store types (e.g., grocery store, fast food outlet, convenience store), but recent recommendations have called for evaluation of in-store food environment to increase precision of exposure given the variety of food options available within store types [31]. Of particular interest, the “Four Ps of Marketing” (Product, Place, Price, Promotion) are demonstrated to impact consumer purchasing behaviour, including food purchasing [4]. Thus, our investigation aimed to evaluate the *in-store retail food environment* in the province of Quebec. We obtained in-store food product and marketing information for the province from a digital marketing database (ScanTrack) purchased from the Nielsen Corporation for the period of 2008–2012. This database assessed weekly consumer purchases and marketing activities of consumer-packaged goods and fresh produce in a representative sample of food retail outlets in Quebec. Retailers consisted of grocery stores, mass merchandisers and convenience stores. Retailer locations are represented using forward sortation areas (FSAs), which are geographic regions defined by the first 3 digits of Canadian postal codes. In Quebec, FSAs identify a section of a major metropolitan area, a medium-sized city, or a specific rural region [32]. The database consists of every Universal Product Code (UPC) within several food categories, although product availability for each food category varied between retailer types. Our analysis evaluated retail food environment measures for 3 categories: vegetables, soft drinks, and ice cream. Vegetables and soft drinks are food products that have both beneficial and adverse, respectively, links with BMI and cardiometabolic diseases and are common targets

for dietary interventions. Ice cream was selected for investigation as it is one of the most hedonic and rewarding commercial food products [33] and so was anticipated to be a particularly strong candidate for interaction with the *Taq1A* genotype, which exerts its effects through the brain's reward system.

For each UPC in the retail database, the following information is available: weekly price and in-store promotion, item description, brand name, package size, and the number of individual items within the pack. Number of servings per unit was calculated using Food and Drug Administration (FDA) data on average serving size and unit package size. We applied methods outlined by Ma et al. [34] to create retail food environment measures, shown in Table 1. Briefly, *regular price per serving* has been derived from the weighted average of the highest price of each UPC within the category over a 3-month moving window across stores [35]. *Frequency of price promotion (discounts)* was obtained from the weighted average number of weeks in which the price of a given UPC was at least 2 standard deviations below its average price [36]. In both cases, overall market shares of each UPC in the entire period (2008–2013) within their category were used as weights. *Non-price promotion (in-store food displays)* is the proportion of products (UPCs) within a target food category that was on display (e.g., end of aisles displays) in a given week in a given store [37]. *Variety* is operationalized as the average number of different Stock Keeping Units (SKU; a number that uniquely identifies distinct products and package sizes) within product categories across stores. Separate investigations have utilized this source of Quebec retail food environment data and have demonstrated that the retail measures are predictive of consumption of specific food products [34] and also can be used for neighbourhood level surveillance of food purchasing [38]. Frequency of in-store display (non-price promotion), discount frequency (price promotion), regular price, and number of SKU (variety) for the vegetable, soft drink, and ice cream categories were used as measures of retail food environment exposures and were assessed as continuous variables.

Assessment of Diet Quality

The Canadian adaptation of the Healthy Eating Index 2010 (HEI-C) was calculated from food and nutrient data derived from the DHQ and served as our outcome measure of diet quality. The HEI-C continuous scoring system was recently described, and a significant inverse association between HEI-C score and obesity risk was recently reported among Canadians [39]. The HEI-C con-

Fig. 1. Data sources and linking.

sists of an adequacy sub-score comprised of 8 adequacy components (total fruits and vegetables, whole fruit, greens and beans, whole grain, dairy, total protein foods, seafood and plant proteins, and fatty acids), as well as a moderation sub-score comprised of 3 moderation components (refined grains, sodium, and empty calories) for a combined total of 11 dietary components. The standard scoring is based on age- and sex-specific serving recommendations found in the 2007 Canada Food Guide. The HEI-C score ranges from 0 to 100, with higher scores indicating better diet quality.

Genotyping

Genome-wide genotyping was performed using a combination of the UK Biobank Axiom Array [40] as well as in-house genotyping projects led by CARTaGENE. Genotyping data for the *DRD2/ANKK1 Taq1A* variant (rs1800497) was extracted using PLINK 1.7 software. As a dominant mode of inheritance has been demonstrated for this particular variant, participants were grouped as carriers if they carried 1 or 2 copies of the minor (A) allele, and as non-carriers if they were homozygous for the major (G) allele.

Data Linkage and Statistical Analysis

Figure 1 illustrates the 3 sources of data that were linked for this analysis: the CARTaGENE biobank, the retail food environment dataset, and Canadian Census data (years 2006 and 2011). Census data according to participants' postal codes was obtained from Statistics Canada in order to account for demographic factors of neighbourhoods that have been associated with differences in residential food environment [3]. The retail food environment data was linked to CARTaGENE participants according to matched FSA to provide estimates of in-store retail food environment exposures at the level of FSA (i.e., neighbourhood retail food environment). Exponential smoothing of the retail variables by quarter was performed to allow the usage of the retail data for the full period of 2008–2012 (up to the year of dietary assessment in CARTaGENE). This technique weighs recent data more heavily than older data when averaging over a period of time and so enabled complete usage of available data. The retail data were temporally and geospatially linked to CARTaGENE data based on the year and quarter (as a proxy for season) of data collection and FSA, respectively.

Upon data linkage, a maximum of $n = 3,532$ participants were available for analysis, although individual sample sizes varied for

each retail food measure according to data availability (see Results section). A χ^2 test with 1 degree of freedom was conducted to assess Hardy-Weinberg equilibrium of the *Taq1A* variant. Misreporting of energy intake (EI) on the FFQ was assessed by comparing the reported EI and estimated energy requirement (EER) for each participant [41, 42]. Participants' weight, height, and age were used to derive individual basal metabolic requirement using the Mifflin-St Jeor equation. The individual EER was then assessed using basal metabolic requirement and available estimate of physical activity level collected by CARTaGENE [43]. Participants were categorized into under-reporter, over-reporter or plausible-reporter based on the ratio of EI:EER, and this variable was included as a covariate in statistical models. A recent investigation demonstrated that adjustment for energy misreporter status as opposed to removal of misreporters from analyses is more appropriate when BMI and adiposity outcomes are evaluated, as overweight/obese individuals are more likely to be energy under-reporters [41]. While our outcome variable of interest was diet quality, adjustment for energy misreporter status as opposed to participant exclusion enabled preservation of our sample size for analyses.

Inverse probability weighting was performed to minimize the risk of bias owing to missing retail data for the food environment measures. The odds of participants missing retail data for our product categories of interest was modelled in relation to our outcome variable (diet quality) and all predictor variables in statistical models. In particular, population density (2011 Census) and socioeconomic characteristics of the residential neighbourhoods according to FSA (% high school completion, median household income, prevalence of low income, % immigrants, and employment rate [2006 Census as not available from 2011 Census]) were assessed for their associations with missing retail data. Predictors that were significantly associated with missing retail data were used to obtain a probability of missing retail data, and the inverse of the probability was used as weight in the respective analyses.

Generalized linear models accounting for spatial clustering by FSA through the use of Generalised Estimating Equations estimation were conducted to assess each outcome measured as a function of retail food environment exposure (in-store display frequency, discount frequency, regular price, number of SKU), genotype (*Taq1A* carrier or non-carrier), and their interaction terms. Analyses were conducted using the GENMOD Procedure in SAS

Table 2. Participant characteristics (*n* = 3,532)

Characteristic	Descriptive statistics ^a
Age, years	55.03 (7.61)
Male gender, <i>n</i> (%)	1,651 (46.74)
Ethnicity (Caucasian), <i>n</i> (%)	3,393 (96.06)
Household income, <i>n</i> (%)	
<CAD 25,000	279 (7.90)
CAD 25,000–50,000	803 (22.73)
CAD 50,000–75,000	804 (22.76)
CAD 75,000–150,000	1,242 (35.16)
>CAD 150,000	404 (11.44)
Education, <i>n</i> (%)	
Less than high school	48 (1.36)
High school	702 (19.88)
College	1,139 (32.25)
University	1,166 (33.01)
Graduate studies	477 (13.51)
Language (French), <i>n</i> (%)	2,385 (95.84)
Smoking status, <i>n</i> (%)	
Non-smoker	3,034 (85.90)
Occasionally	115 (3.26)
Daily	383 (10.84)
BMI	27.63 (5.43)
Taq1A carrier, <i>n</i> (%)	1,185 (33.5)
Diet quality scores (min.–max.)	
HEI C2010 score (0–100)	59.37 (13.73)
Adequacy sub-score (0–60)	37.14 (13.93)
Moderate sub-score (0–40)	25.51 (4.82)
Retail food environment measures (min.–max.)	
Ice cream variety (0–325.79)	111.98 (117.51)
Ice cream discount frequency (0–0.67)	0.26 (0.14)
Ice cream in-store display (0–0.33)	0.10 (0.08)
Ice cream regular price per serving (0.32–1.30)	0.45 (0.15)
Vegetable variety (0–512.48)	193.50 (209.29)
Vegetable discount frequency (0–0.60)	0.36 (0.14)
Vegetable in-store display (0–1)	0.10 (0.17)
Vegetable regular price (per serving) (0.05–2.77)	0.49 (0.62)
Soft drink variety (0–290.10)	138.91 (81.32)
Soft drink discount frequency (0–0.64)	0.21 (0.14)
Soft drink in-store display (0–0.72)	0.14 (0.15)
Soft drink regular price (per serving) (0.25–0.80)	0.40 (0.13)

^a Values are mean (SD) unless otherwise indicated.

9.4 (SAS Institute Inc., Cary, NC, USA). The models were adjusted for age, sex, ethnicity (Caucasian vs. non-Caucasian), CARTaGENE region, season of dietary assessment completion, annual household income, language in which the questionnaire was completed (English or French), EI, participant's energy misreporting status, and for the following Census variables: neighbourhood prevalence of low-income households, percent immigrant status, employment rate, population density, and proportion of high school completion. All reported *p* values are two-sided and the Bonferroni-corrected alpha level for statistical significance was 0.0042 (0.05/12 statistical models).

Fig. 2. CARTaGENE FSAs represented in Quebec retail food environment data.

Results

Participants' characteristics for the maximum available sample are presented in Table 2. Participants were approximately 55 years old on average, with a roughly equal proportion of men and women (47% male). Approximately half of the analytical sample reported earning an annual household income of $\geq$ CAD 75,000. The majority of participants were Caucasian (96%) and completed study questionnaires in French (96%). The *Taq1A* variant was in Hardy-Weinberg equilibrium ($\chi^2 = 1.67$, $p = 0.20$), and 33.5% of participants were carriers of the *Taq1A* allele, similar to the population frequency reported in other studies [29]. The mean BMI was 27.6 and the mean HEI-C score was 59.4. Table 2 also reports summary statistics for the retail food environment measures, including means $\pm$ standard deviations of the number of food products in each category (variety), means $\pm$ standard deviations of the regular price per serving, the percentage of time the product categories were on price promotion (discount), and the percentage of time the product categories were promoted with in-store displays (non-price promotion). Table 3 presents mean HEI-C scores per HEI-C quartile (lowest to highest score) for both the overall score and its individual components. Upon geospatial linkage of the CARTaGENE data with

Table 3. Mean values of HEI-C individual components and overall score ($n = 3,532$)

Components	Standard for max. score	HEI-C 2010 score quartile (poorest to highest quality)				<i>p</i> value
		1	2	3	4	
HEI-C 2010 score, ranges	0–100	≤54.33	54.33–63.22	63.22–68.64	≥68.64	
Fruit and vegetables, servings/day	7–8	5.23	6.66	8.09	9.00	<0.0001
Whole fruit, servings/day	1.47–1.68	1.33	1.87	2.63	3.09	<0.0001
Greens and beans, servings/day	0.735–0.84	0.47	0.87	1.26	1.44	<0.0001
Whole grains, servings/day	3–4	0.45	0.53	0.58	1.05	<0.0001
Dairy, servings/day	2–3	1.59	1.63	1.63	1.79	0.0279
Total protein foods, servings/day	2–3	3.32	3.76	4.27	4.67	<0.0001
Seafood and plant protein, servings/day	0.64–0.96	0.35	0.60	0.85	1.06	<0.0001
Fatty acids, (PUFA + MUFA)/SFA	2.5	1.29	1.80	1.97	2.21	<0.0001
Refined grains, servings/day	<50% grain refined	2.32	2.55	2.53	2.26	<0.0001
Sodium, mg/day	AI	2,178.27	2,392.26	2,446.06	2,277.29	<0.0001
Empty calories, % energy	≤19% of energy	22.77	15.73	12.72	10.89	<0.0001

AI, adequate intake.

Table 4. Summary of genotype and retail food measures main and interaction effects

Retail food environment measure	<i>n</i>	Retail measure main effect			Retail measure × <i>Taq1A</i> interaction		
		estimate	95% CI	<i>p</i> value	estimate	95% CI	<i>p</i> value
Vegetable display	1,930	−2.35	(−5.85, 1.16)	0.1893	3.40	(−4.66, 11.46)	0.4083
Vegetable regular price	1,930	−1.05	(−1.78, −0.33)	0.0042	2.46	(0.78, 4.14)	0.0041
Vegetable discount frequency	1,930	0.51	(−3.87, 4.89)	0.8183	−2.14	(−10.45, 6.16)	0.6129
Vegetable variety	3,531	−0.0004	(−0.0023, 0.0016)	0.7244	−0.002	(−0.006, 0.001)	0.1463
Ice cream display	1,960	6.54	(−0.72, 13.8)	0.0775	−15.46	(−24.83, −6.10)	0.0012
Ice cream regular price	1,960	−0.25	(−3.79, 3.29)	0.8900	2.82	(−3.95, 9.59)	0.4146
Ice cream discount frequency	1,960	−1.04	(−5.84, 3.77)	0.6730	−1.84	(−9.03, 5.36)	0.6171
Ice cream variety	3,531	−0.001	(−0.005, 0.002)	0.5307	−0.003	(−0.009, 0.003)	0.3409
Soft drink display	3,442	−5.19	(−11.52, 1.13)	0.1077	0.77	(−9.09, 10.63)	0.8782
Soft drink regular price	3,442	3.50	(−6.01, 13.02)	0.4703	−2.99	(−15.19, 9.21)	0.6308
Soft drink discount frequency	3,442	−3.57	(−12.56, 5.42)	0.4368	−6.56	(−18.74, 5.63)	0.2916
Soft drink variety	3,531	−0.002	(−0.007, 0.004)	0.5360	−0.006	(−0.014, 0.002)	0.1407

the marketing data by FSA, $n = 207$ FSAs were shared representing coverage of over 90% of the CARTaGENE biobank (Fig. 2).

There was no statistically significant association between *Taq1A* genotype and diet quality (estimate: −0.02 [95% CI: −0.74, 0.70], $p = 0.9523$). In general, no statistically significant main effects were observed between the retail food environment measures and diet quality, with the exception of regular price of vegetables (Table 4). For this retail measure, a significant inverse association was observed ($p = 0.0042$), indicating that a higher price of vegetables was associated with a poorer diet quality when

genotype was not considered. When interactions between the retail food environment measures and *Taq1A* genotype were evaluated, 2 statistically significant results were observed. A significant interaction between genotype and ice cream display was observed such that allele carriers with increasing exposure to in-store display of ice cream products had a significantly lower mean HEI-C score compared to allele carriers who had lower exposure to the in-store displays ($p = 0.0012$). Figure 3 illustrates the predicted HEI-C score for each genotype group according to different levels (high/average/low) of in-store ice cream display exposure as a standardized variable. The graph

Fig. 3. Predicted HEI-C scores for high/average/low values (mean $\pm$ 1 standard deviation) of retail food measure exposures.

indicates that non-carriers had similar diet quality scores regardless of exposure level to in-store ice cream displays (Fig. 3a). A significant interaction was also observed between genotype and vegetable regular price such that allele carriers with increasing exposure to higher priced vegetables had significantly higher mean HEI-C score compared to allele carriers who had exposure to lower priced vegetables ($p = 0.0041$). Non-carriers demonstrated an opposite pattern of responsivity, having a higher HEI-C score at lower exposure level of standardized vegetable price (Fig. 3b). The interaction terms for the remaining retail food environment measures were not statistically significant.

Discussion

While we observed no significant main effect of the *DRD2/ANKK1 Taq1A* polymorphism on diet quality, we report novel statistically significant interactions between genotype and certain retail food environment measures on this dietary outcome. Diet quality scores among carriers of the *Taq1A* allele displayed a differential pattern of responsivity to in-store displays of ice cream and regular prices of vegetables, where higher exposure to ice cream displays was associated with a poorer diet quality and exposure to higher prices of vegetables was associated with a better diet quality. Non-carriers did not display this pattern. Diet quality scores among this group were similar regardless of exposure to ice cream displays, and scores were higher with exposure to lower prices of vegetables. To our knowledge, this is the first investigation to evalu-

ate gene-by-environment interactions on diet quality. Our findings add to a nascent but growing evidence base that supports the argument that genetic variation modifies individual responsivity to environmental exposures and, thus, may enable future development of individualized strategies to promote healthful dietary choices.

The *DRD2/ANKK1 Taq1A* locus is a candidate gene for neurobehavioural genetic differential susceptibility, and taken altogether our findings reflect the “for better and for worse” pattern of adaptive environmental responsivity proposed by the hypothesis. *Taq1A* allele carriers exposed to a negative environmental exposure (more ice cream displays) demonstrated poorer dietary quality than non-carriers, but allele carriers also demonstrated significantly better dietary quality than non-carriers when exposed to a potential perceived supportive environment (vegetable regular prices). Our finding of an inverse significant interaction between the *Taq1A* polymorphism and in-store displays of ice cream on diet quality reflects a previous association of this polymorphism with less healthful eating behaviour [28]. Yet, our investigation extends the previous work in an important way to suggest that adverse eating outcomes associated with this polymorphism may be limited to conditions of less healthful environmental exposures and that a healthier environment may lead to adaptive positive behavioural outcomes among this genetic subgroup. The interpretation of our finding of a positive significant interaction between the *Taq1A* polymorphism and vegetable price on diet quality requires consideration of research outside of traditional nutritional science. To note first, the statistically significant inverse main association between regular price of vegetables and diet quality is

in line with previous research that has identified price as a barrier to healthful eating [44]. Indeed, when considering interactions with genotype, non-carriers displayed a pattern of responsivity to vegetable prices in this anticipated direction (higher HEI-C score with lower prices). However, we also observed that *Taq1A* carriers respond to a higher price of vegetables in a nutritionally beneficial way. While perhaps not intuitive initially, neuroeconomic research has identified price as a point of purchase, value reward-generating signal, and subgroups of individuals express increased willingness to pay in response to higher price stimuli due to a perception of higher quality [45, 46]. A possible explanation of our finding is that *Taq1A* allele carriers may be more responsive to a higher price as a signal of higher quality and, therefore, experience a reward-generating effect from this marketing stimulus rendering them more likely to purchase, and perhaps subsequently consume, higher priced vegetables. In this context, the quality signalling value of price for vegetables, an example of low energy density foods, might have been impactful in terms of positive behavioural responsiveness for the *Taq1A* carrier subgroup. While previous research has linked genetic variation to financial risk taking [47], the role of specifically the *Taq1A* polymorphism has not been evaluated in such a context. Further investigation of this polymorphism in the context of economic-related decision-making is needed to confirm our proposed explanation for our price finding.

The neurobehavioural genetic differential susceptibility hypothesis is worthwhile to expand upon as recent studies have begun to evaluate its role in nutrition and metabolic health outcomes. A recent study demonstrated a differential pattern of association between the dopamine D4 receptor gene (*DRD4*) 7-repeat allele and socioeconomic conditions on total fat intake among girls [22]. Allele carriers in poor socioeconomic conditions had higher total fat intake, while carriers in higher socioeconomic conditions had significantly lower total fat intake. Non-carriers had similar intakes of total fat regardless of socioeconomic condition. Another study explored the relationship between external eating, one's tendency to eat in response to external food cues, retail food environment exposures, and dietary patterns in children [6]. In that investigation, the individual trait of external eating served as a proxy for differential susceptibility genetics as genetic data was not available. The authors reported that in-store food displays in the retail food environment significantly altered healthful food consumption among children with a high external eating score. Children with a higher tendency for external eating who were exposed to a high degree of healthful (veg-

etables) and low degree of unhealthful (soft drinks) in-store food displays had a more healthful food consumption compared to children who had a lower tendency for external eating [6]. Both of these investigations support the argument that individual factors, including genetics, modify responsivity to environmental exposures to influence dietary outcomes, and the results of our present investigation further add to this evidence base.

Our investigation possessed a number of strengths, including the unique linkage of genetic data with retail food environment data to evaluate the underexplored area of gene-environment interaction. In our case, environment was assessed as a naturalistic, true form of environment through everyday exposures to retail food activities in one's neighbourhood. In particular, we assessed 3 aspects of the "Four Ps of Marketing" associated with consumer food purchasing. We utilized robust analytical approaches to enable maximum data usage and to account for several potential biases and confounding variables. Our statistically significant results also met the stringent Bonferroni-corrected *p* value of 0.0042. Despite these strengths, as this study is observational in nature, the potential for residual confounding cannot be ruled out. While our data was obtained from population sources, the results are only generalizable to our study population mainly comprised of middle-aged Caucasian, middle class, and educated participants. Other limitations include the assessment of a single genetic variant, reliance on self-reported dietary data, and attention to only 3 food categories. We were limited in our ability to assess a more comprehensive number of genetic variants as most candidate genes for differential susceptibility are variable number tandem repeats and, as a result, not available on genome-wide genotyping platforms that measure SNPs. In addition, the limitations associated with self-reported dietary data, particularly from FFQs, are less impactful to our investigation as diet quality was our outcome variable and was constructed by assessing patterns of food intake rather than reliance on nutrient intakes alone [48]. Finally, although we evaluated only 3 food categories, these categories were strong candidates for investigation due to their established links with cardiometabolic health (vegetables and soft drinks) or rewarding properties (ice cream). While it is warranted for future work to assess interactions of genetic variations with the retail food environment more comprehensively, and in a manner more reflective of the real-life experience (simultaneous exposure to numerous in-store food cues), our study responds to recent calls to improve measures of the food environment by assessing in-store food products and marketing strategies [3].

Conclusions

In conclusion, we report novel interactions between the *Taq1A* polymorphism and retail food environment exposures on diet quality. Our findings add to an evidence base that supports the position that genetic variation may influence adaptive responsivity to the environment and subsequently influence dietary outcomes. These results hold relevance for researchers investigating novel strategies aimed at targeting individual food cue responsiveness [49].

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Statement of Ethics

This secondary analysis of CARTaGENE data was approved by the CARTaGENE SDAC, and ethics approval for this analysis was obtained from the McGill University Faculty of Agriculture and Environmental Sciences Research Ethics Board. Informed consent was obtained from CARTaGENE participants at the time of study participation by the cohort's investigative team.

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Disclosure Statement

The authors declare that they have no competing interests.

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Author Contributions

D.E.N. conceived the original idea for the investigation, provided guidance on statistical analyses, and drafted the manuscript. Y.H. conducted the statistical analyses. C.P. and A.K.P. provided guidance on statistical analyses. Y.M. and L.D. provided access to the retail food environment data. Y.H., C.P., A.K.P., Y.M. and L.D. contributed to the manuscript revision for important intellectual content. All authors read and approved the final manuscript.

Availability of Data and Materials

Data described in the manuscript, code book and analytic code will be made available upon request pending approval by CARTaGENE's SDAC.

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