ORIGINAL INVESTIGATION

Genetic Differential Susceptibility to Socioeconomic Status and Childhood Obesogenic Behavior
Why Targeted Prevention May Be the Best Societal Investment

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IMPORTANCE Genes may work by modulating the way individuals respond to environmental variation, and these discrete and differential genes vs environmental interactions may not be readily captured in simple association studies.

OBJECTIVE To determine whether children carrying the 7-repeat allele of the DRD4 gene living under adverse economic conditions have worse-than-average fat intake compared with those living in a healthy environment.

DESIGN, SETTING, AND PARTICIPANTS Data from an established prospective birth cohort (Maternal Adversity, Vulnerability, and Neurodevelopment) were used to study 4-year-old children from Montreal, Quebec, Canada and Hamilton, Ontario, Canada. A total of 190 children (94 girls and 96 boys) had height and weight measured and complete food diaries and were therefore eligible for the study. The study is derived from a birth cohort started in June 2003 and still ongoing. The last age of follow-up was at 6 years.

EXPOSURES Social environment was characterized based on the gross family income, and DNA was genotyped for the 7-repeat allele of the DRD4 gene.

MAIN OUTCOMES AND MEASURES Fat intake.

RESULTS The 5 steps to distinguish the differential susceptibility from other types of interaction were followed, and the study confirms that differential susceptibility is a relevant model to address the association between the 7-repeat allele of DRD4 and food choices in girls. Of the 190 children, 112 did not have the DRD4 7-repeat allele and 78 did. Baseline characteristics did not differ in these 2 groups. Although not different in several confounders, such as maternal educational level, maternal smoking during gestation, birth weight, and breastfeeding duration, girls carrying the 7-repeat allele of the DRD4 gene and living in adverse socioeconomic conditions have increased fat intake compared with girls who are noncarriers (DRD4 7+ mean, 33.95% of calories derived from fat; 95% CI, 28.76%-39.13%; DRD4 7− mean, 28.76%; 95% CI, 26.77%-30.83%). However, girls carrying the 7-repeat allele of the same gene and living in better socioeconomic conditions have decreased fat intake compared with noncarriers (DRD4 7+ mean, 29.03% of calories derived from fat; 95% CI, 26.69%-31.51%; DRD4 7− mean, 31.88%; 95% CI, 30.28%-33.58%).

CONCLUSIONS AND RELEVANCE Alleles previously considered to be obesity risk alleles might in fact function as plasticity alleles, determining openness to environmental modification and/or intervention, as seen in the girls in this study. This finding has important implications for obesity prevention and social pediatrics.

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enome-wide association studies\textsuperscript{1,2} have been successful in identifying several genes associated with obesity. However, genes may vary by modulating the way individuals respond to environmental variation, and these discrete and differential genes vs environmental interactions may not be readily captured in simple association studies. In addition, to date, most of these studies focused on body mass index (not food intake or energy expenditure) as the outcome, which may not be informative in terms of identifying vulnerability and proposing preventive measures.

The differential susceptibility hypothesis\textsuperscript{3,4} suggests an alternative approach to genetic association studies that may have particular utility for common, complex diseases, such as obesity. From an evolutionary perspective, the genetic differential susceptibility hypothesis proposes that, as a form of bet-hedging against an uncertain future, natural selection has maintained genes for both conditional (shaped by the environment) and alternative (fixed) health strategies.\textsuperscript{5} In other words, individual variations in the magnitude of biological responses regulate openness or susceptibility to environmental influences, ranging from particularly harmful under unfavorable conditions to especially responsive to favorable environments.\textsuperscript{4}

Research on the differential susceptibility hypothesis has thus far almost exclusively focused on socioemotional and cognitive-developmental outcomes, indicating that plasticity genes vary in relation to how much carriers (compared with noncarriers) are negatively affected by environmental adverse events\textsuperscript{6,7} and how much they benefit from support\textsuperscript{3,4,8,9}. A recent study\textsuperscript{10} found an association between the social environment and telomere length, moderated by genetic variation within the serotonin and dopamine pathways. Of interest, at the same time that dopamine-related genes form one of the main groups of genes that influence neurocognitive outcomes, they also underlie motivated behaviors and decision-making processes, which are known to be involved in eating choices.

Considering the differential susceptibility hypothesis\textsuperscript{11} and the association between the 7-repeat allele of \textit{DRD4} (OMIM 126452) with maladaptive eating,\textsuperscript{12-14} we hypothesized that children carrying the 7-repeat allele living under adverse social and economic conditions would have worse-than-average maladaptive eating. On the other hand, children carrying the 7-repeat allele living in a healthy, nonadverse environment would actually have better-than-average food choices.\textsuperscript{15}

### Methods

We used data from an established prospective birth cohort (Maternal Adversity, Vulnerability, and Neurodevelopment Study [MAVAN]).\textsuperscript{16,17} The study sample included 4-year-old children from Montreal, Quebec, Canada, and Hamilton, Ontario, Canada. Children came to the laboratory for various food-related measures and had their standing height, without shoes, measured (to the nearest 0.1 cm) with a stadiometer (PE-AIM-101; Perspectives Enterprises). Body weight, with participants in light clothing, was measured (to the nearest 0.1 kg) with a digital floor scale (Tanita Body Fat Monitor BF-625; Tanita). Body mass index was calculated as weight in kilograms divided by height in meters squared.

Approval for the MAVAN project was obtained from obstetricians who performed deliveries at the study hospitals and by the ethics committees and university affiliates (McGill University and Université de Montréal, the Royal Victoria Hospital, Jewish General Hospital, Centre hospitalier de l’Université de Montréal, and Hôpital Maisonneuve-Rosemont) and St Joseph’s Hospital and McMaster University, Hamilton, Ontario, Canada. Written informed consent was obtained from all participants.

A total of 190 children (94 girls and 96 boys) had complete food frequency questionnaires for analysis, valid for the local population.\textsuperscript{18} The study is derived from a birth cohort started in 2003 and still ongoing. The last age of follow-up was at 6 years. On the basis of these questionnaires, the quantitative analysis of total caloric and macronutrient intake is derived using NutriBase software, version NB7 (CyberSoft Inc). In this data analysis, we studied the percentage of calories derived from fat reported on the questionnaires. The social environment was characterized based on the gross family income, categorized according to the low income cutoff Index (LICO)\textsuperscript{19} into below or above the LICO.

Saliva samples were collected, and genotyping of the DNA was performed masked to the children’s behavior and phenotype. The 48-base pair variable number of tandem repeats region in the third exon of \textit{DRD4} was amplified with polymerase chain reaction techniques with primers and conditions previously described.\textsuperscript{20} Statistical analysis of the baseline characteristics was performed using the \textit{t} test for continuous data and the \textit{χ}\textsuperscript{2} test for categorical variables.

The genetic model was driven by the biological function because the 7-repeat allele is markedly hypofunctional relative to all other alleles. Thus, it is presence or absence of this allele that affects the phenotype (dominant model).\textsuperscript{21} On the basis of the genotype (7-repeat allele present or absent) and the income categories (above or below LICO), analysis of covariance was performed adjusting for body mass index as a covariate. The \textit{χ}\textsuperscript{2} test of interaction and association between the 7-repeat allele of \textit{DRD4} and food choices in girls.

### Key Points

**Question:** Does the 7-repeat allele of \textit{DRD4} that is associated with maladaptive eating exhibit differential susceptibility effects under adverse vs healthy environments?

**Findings:** The study confirms that the differential susceptibility is a relevant model to address the association between the 7-repeat allele of \textit{DRD4} and food choices in girls.

**Meaning:** The results underscore the possibility of going beyond the one-size-fits-all approach to childhood obesity prevention and moving toward better targeted approaches that focus on populations that are particularly genetically vulnerable to a disadvantaged social environment and more responsive to interventions that foster more favorable conditions.
smoking during gestation, and poor maternal care; analysis was performed again using different outcomes (sugar and percentage of protein consumed). Data were analyzed using SPSS software, version 18.0 (SPSS Inc). Significance levels for all measures were set at \( P < .05 \).

### Results

Children with or without the 7-repeat genotype did not differ in many confounders (Table), such as maternal educational level, maternal smoking during gestation, birth weight, and breastfeeding duration. However, girls carrying the 7-repeat allele of the \( DRD4 \) gene and living in adverse socioeconomic conditions have increased fat intake compared with girls who are noncarriers (\( DRD4 \) 7+ mean, 33.95% of calories derived from fat; 95% CI, 28.76%-39.13%; \( DRD4 \) 7− mean, 28.76%; 95% CI, 26.77%-30.83%). Girls carrying the 7-repeat allele of the same gene and living in better socioeconomic conditions have decreased fat intake compared with noncarriers (\( DRD4 \) 7+ mean, 29.03% of calories derived from fat; 95% CI, 26.69%-31.51%; \( DRD4 \) 7− mean, 31.88%; 95% CI, 30.28%-33.58%).

To test our hypothesis, we followed the model proposed by Belsky et al. According to this model, there are 5 steps to distinguishing true differential susceptibility from other types of interaction. Step 1 consists of the application of conventional statistical criteria for evaluating genuine moderation (crossover interaction). In our data, an initial 3-way analysis of variance revealed an interaction among sex, \( DRD4 \) genotype, and income on fat intake (for those raised in poorer conditions: boys: \( DRD4 \) 7+ mean, 776.82 calories derived from fat; 95% CI, 766.82-786.82; \( DRD4 \) 7− mean, 647.40 calories derived from fat; 95% CI, 637.40-657.40). Step 2 is a test of the association between the susceptibility factor and the outcome should be performed; if the association is nonzero, there is no support for differential susceptibility. In our findings, the Phi and Cramer's V tests are significant at \( P = .005 \) on the percentage of intake of calories derived from fat in girls (Figure 1).

In step 2, the aim is to distinguish differential susceptibility from other gene-environment correlations that may reflect rearing experiences evoked by the genotypes to show that the susceptibility factor (income) and the predictor (\( DRD4 \) genotype) are independent. Indeed, in our data, a nonsignificant \( \chi^2 \) at \( P = .58 \) demonstrates that these variables are independent.

In step 3, a test of the association between the susceptibility factor and the outcome should be performed; if the association is nonzero, there is no support for differential susceptibility. In our findings, the Phi and Cramer’s V tests are equal to 0, supporting the differential susceptibility.

Step 4 is a comparison of the regression plot with the prototypical graphic representing differential susceptibility. As seen in Figure 2, the plot from the preliminary data is similar to the prototypical graphic representing differential susceptibility.

Finally, in step 5, the specificity of the model should be tested by replacing susceptibility factors and outcomes. Indeed, changing the susceptibility factor to being born with intrauterine growth restriction (interaction \( P = .38 \), a mother who smoked during gestation (interaction \( P = .77 \)), or a mother reporting low parental bonding (interaction \( P = .93 \)), cannot elicit the differential susceptibility findings regarding \( DRD4 \) genotype and fat intake. Changing the outcome to consumption of sugars (interaction \( P = .35 \)) or percentage of calories derived from protein (interaction \( P = .46 \)) similarly does not elicit the differential susceptibility findings regarding \( DRD4 \) genotype, suggesting that the differential susceptibility model for \( DRD4 \) genotypes (7+ or 7−) and income variation on the percentage of fat consumed at 4 years of age in girls is specific.

### Discussion

The 5 steps proposed by Belsky et al to distinguish the differential susceptibility from other types of interaction were followed, and the study confirms that the differential susceptibility is a relevant model to address the association between...
the 7-repeat allele of DRD4 and food choices in girls. In other words, the previously considered obesity risk alleles might in fact function as plasticity alleles, determining openness to environmental modification and/or intervention. Shifting from a vulnerability to a differential susceptibility paradigm not only enables the study of the full range of negative and positive gene vs environmental interactions but also has the potential to bring more impactful and better targeted intervention to improve developmental and health outcomes to the individuals who are also the most vulnerable. We focused on the DRD4 polymorphism for the association of this gene variant with obesity risk, which has been extensively studied by our group,\(^\text{13,14,25}\) and for the evidence that DRD4 could function as a plasticity gene in neurocognitive outcomes.\(^\text{8,26}\) Further studies may explore the effect of other dopamine polymorphisms in these aspects.

Of interest, the effect is exclusively found in girls. The reported gene vs environment interaction could be adaptively more important for females, especially considering reproductive strategies in adverse environments. Alternatively, it is possible that at this age the effect is not seen in boys because growth in general and specifically the adiposity rebound occur at different ages according to sex,\(^\text{27}\) and these events influence appetite.\(^\text{28,29}\) The sex-specific neurodevelopmental course or adaptive strategy could make girls more prone to show systematically greater biological sensitivity at different ages and to a variety of social contexts. Finally, considering the literature reporting differences in the brain processing and behavioral responses to feelings of hunger and satiation,\(^\text{30,31}\) as well as food preferences,\(^\text{32}\) in females vs males, such gene vs environmental interactions may as well be sex specific, especially at this age.\(^\text{33,34}\) Another study\(^\text{35}\) reported sex differences in the differential susceptibility findings. Although future research is needed to elicit further genetic differential susceptibility in both sexes, the present results of maladaptive eating in girls before obesity has taken place may inform obesity prevention and primary pediatric care.

Our study has some limitations, such as the sample size; these results should be replicated in larger samples. In addition, our study was performed in a country where there is not a large variation in terms of socioeconomic status. Replication in places of extreme socioeconomic inequalities will be informative.

There are large disparities in the nutritional quality of the food environment between individuals and neighborhoods from low and high socioeconomic statuses. Food-related marketing activities,\(^\text{36}\) convenience stores,\(^\text{37}\) and fast-food outlet availability near schools\(^\text{38}\) are more prevalent in neighborhoods with low compared with high socioeconomic statuses. Considering that poor diet and obesity are critical risk factors for diabetes mellitus, cardiovascular disease, and other chronic diseases that make up the greatest share of health care expenses,\(^\text{39}\) this may render even more pressing the recommendation for society to prioritize human capital investment in fighting poverty earlier rather than later in life.\(^\text{40}\)
Conclusions

The results of this study underscore the possibility of going beyond the present one-size-fits-all approach to childhood obesity prevention and moving toward better targeted approaches that focus on populations that are particularly genetically vulnerable to disadvantaged social environments and more responsive to interventions that foster more favorable conditions, be they environmental or individual. Efforts have been made to test this possibility and find support for the genetic moderation of intervention efficacy in a manner consistent with the differential susceptibility concept.\(^4^1\),\(^4^2\) By studying socioeconomic status within a framework that accounts for the complex interplay among human brain, biology, and society, we hope to inform rational and targeted design of intervention.

REFERENCES


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