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Association between olfactory receptor genes, eating behavior traits and adiposity: Results from the Quebec Family Study

Anne C. Choquette [a,b], Luigi Bouchard [c,d], Vicky Drapeau [e], Simone Lemieux [b,f], Angelo Tremblay [a], Claude Bouchard [g], Marie-Claude Vohl [b,f], Louis Pérusse [a,b,*]

[a] Department of Social and Preventive Medicine, Laval University, Quebec, Canada
[b] Institute of Nutraceutical and Functional Foods, Quebec, Canada
[c] Department of Biochemistry, Sherbrooke University, Sherbrooke, Canada
[d] ECOGENE-21, Chicoutimi Hospital, Saguenay, Canada
[e] Department of Physical Education, Laval University, Quebec, Canada
[f] Department of Food Science and Nutrition, Laval University, Quebec, Canada
[g] Pennington Biomedical Research Center, Baton Rouge, LA, USA

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ABSTRACT

Obesity is a major health problem that can be influenced by eating behaviors. Evidence suggests that the sensory properties of food influence eating behaviors and lead to overeating and overweight. A previous genome-wide linkage scan for eating behavior traits assessed with the Three-Factor Eating Questionnaire (cognitive dietary restraint, disinhibition and hunger) performed in the Quebec Family Study (QFS) revealed a quantitative trait locus for disinhibition on chromosome 19p13. This region encodes a cluster of seven olfactory receptor (OR) genes, including *OR7D4*, previously associated with odor perceptions. Direct sequencing of the *OR7D4* gene revealed 16 sequence variants. Nine *OR7D4* sequence variants with minor allele frequency (MAF) > 1% as well as 100 SNPs spanning the cluster of OR genes on 19p13 were tested for association with age- and sex-adjusted eating behaviors as well as adiposity traits in 890 subjects. One *OR7D4* sequence variant (rs2878329 G>A) showed evidence of association with reduced levels of adiposity ($p = 0.03$), cognitive dietary restraint ($p = 0.05$) and susceptibility to hunger ($p = 0.008$). None of the *OR7D4* SNPs was associated with disinhibition, but a SNP (rs2240927) in another OR gene (*OR7E24*) showed evidence of association ($p = 0.03$). Another SNP in the *OR7G3* gene (rs10414255) was also found to be associated with adiposity and eating behaviors. These results are the first to suggest that variations in human olfactory receptor genes can influence eating behaviors and adiposity. The associations reported in the present study should be interpreted with caution considering the number of tests performed and considered as potential new hypotheses about the effects OR polymorphisms on eating behaviors and obesity that need to be further explored in other populations.

1. Introduction

Obesity is one of the most important health issues of the 21th century, with an annual medical cost reaching 147 billion dollars in the USA alone [1]. Several studies suggest that there is a relationship between eating behavior traits and obesity [2]. Accordingly, cognitive dietary restraint has been associated with lower energy intake [3,4], lower weight status [5] and lower energy expenditure [6]. However, this eating behavior has also been associated with increased energy intake in stressful conditions [7] and with weight gain over time [8]. As recently reviewed by Bryant et al., disinhibition has been associated with higher dietary intake, overeating episodes and greater BMI [9]. Eating behaviors are also influenced by genetic factors, both family and twin studies suggesting that there may be significant genetic components to these traits, but that the true magnitude of the genetic variance remains to be properly quantified [10].

There is now considerable evidence showing that hedonic response to the sensory properties of food, such as smell and taste, can influence eating behaviors and lead to overeating and overweight [11–13]. Indeed, sensory perception of food, particularly smell, influences appetite and satiety signals, as well as food choices and food consumption [14]. The mechanism of smell is complex and implies many olfactory receptors. Genes encoding olfactory receptors (OR) represent 3% of our genome, which is the largest family of genes of the human genome. The high phenotypic diversity of olfaction in human is partly due to the high prevalence of genetic variants in OR genes [15]. Accordingly, two individuals having different

* Corresponding author at: Division of Kinesiology, Faculty of Medicine, Laval University — PEPS Bldg., 2300 rue de la Terrasse, Quebec, Canada G1V 0A6. Tel.: +1 418 656 2131x7831; fax: +1 418 656 3044.
E-mail address: louis.perusse@kin.msp.ulaval.ca (L. Pérusse).

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genetic variations on their olfactory receptors could perceive odors differently.

To the best of our knowledge, there is no literature suggesting that variation in OR genes is related to eating behaviors and weight status. However, a recent study from Keller et al. showed for the first time a link between genetic variants in an olfactory receptor and odor perceptions. The latter study examined two non-synonymous SNPs in the *OR7D4* (olfactory receptor family 7 subfamily D member 4) gene, resulting in amino acid changes, R88W and T133M. This study reported that these variants, which are in complete linkage disequilibrium, were responsible for 39% of the variance in smell sensitivity for androstenone, an odorous steroid derived from testosterone. Moreover, subjects who were heterozygous for the variants were more likely to describe the smell of vanillin as "honey", "sweet" and "vanilla" from a list of 146 semantic descriptors [16].

The *OR7D4* gene contains 1 exon encoding a 312 amino acids (939 bp) olfactory receptor selectively expressed in human nasal epithelium [17]. This gene is located in the 19p13 region, which showed an evidence of linkage with disinhibition in a previous genome-wide linkage analysis of eating behavior traits performed in 202 nuclear families from QFS [18].

The objective of the present study was to determine whether DNA sequence variations in the *OR7D4* gene are associated with eating behavior traits (cognitive dietary restraint, disinhibition and hunger). We hypothesize that *OR7D4* sequence variants may play a role in eating behaviors and adiposity related traits. Since *OR7D4* is located within a cluster of seven OR genes, we also tested association with a total of 100 additional SNPs covering the cluster of OR genes on 19p13.

2. Materials and methods

2.1. Subjects

Subjects for this study were participants of QFS. The aim of this prospective family study was to investigate the genetic basis of obesity and cardiovascular and diabetes risk factors [19]. QFS has been approved by the Laval University Medical Ethics Committee and all study participants provided written informed consent. A total of 890 subjects (380 men and 510 women) were included in the present study. Characteristics of the participants are presented in Table 1.

2.2. Adiposity and eating behavior assessment

Body density was obtained by underwater weighing and was converted to percent body fat using the equation of Siri [20]. BMI was derived from body weight divided by height squared (kg/m^2). Waist circumference (WC) was measured according to procedures recommended by the Airlie Conference [21]. Total (TAT), visceral (VAT) and subcutaneous (SAT) abdominal adipose tissue areas were measured by computed tomography with a scan performed at the abdominal level (L4 and L5 vertebrae). Eating behavior traits were assessed by the 51 questions of the Three-Factor Eating Questionnaire (TFEQ) from Stunkard and Messick [22], as validated for French populations [23]. The 3 traits assessed by the TFEQ are cognitive dietary restraint (21 questions), disinhibition (16 questions) and susceptibility to hunger (14 questions). Cognitive dietary restraint is a conscious control over food intake with concerns about shape and weight. Disinhibition is an overconsumption of food in response to stimuli associated with a loss of control. Susceptibility to hunger is the food intake in response to feelings and perceptions of hunger [22].

Table 1
Characteristics of QFS participants.

	Total (n = 890)	n	Men (n = 380)	n	Women (n = 510)	n
Age (years)	43.7 ± 16.8	890	43.7 ± 16.4	380	43.8 ± 17.1	510
Adiposity						
BMI (kg/m^2)	27.9 ± 7.6	890	27.7 ± 6.5	380	28.1 ± 8.4	510
WC(cm)	89.6 ± 18.3	860	94.8 ± 16.7	375	85.5 ± 18.4	485
Body fat (%)	28.4 ± 10.8	720	23.2 ± 9.1	318	32.5 ± 10.3	402
TAT (cm^2)	412.7 ± 225.7	648	357.2 ± 200.1	272	452.8 ± 234.8	376
VAT (cm^2)	119.6 ± 80.8	648	135.5 ± 87.3	272	108.1 ± 73.8	376
SAT (cm^2)	293.1 ± 173.0	640	221.7 ± 134.0	272	344.7 ± 179.8	376
Eating behaviors						
Cognitive dietary restraint	7.3 ± 4.5	667	5.9 ± 3.7	272	8.2 ± 4.8	395
Disinhibition	5.4 ± 3.3	669	4.6 ± 3.0	274	6.0 ± 3.4	395
Susceptibility to hunger	4.0 ± 3.4	668	4.2 ± 3.5	273	4.0 ± 3.2	395

Values are means ± SD.

2.3. Sequencing and genotyping

Direct sequencing of 5′ flanking region (up to 1500 base pairs) and coding regions of *OR7D4* was performed to identify new genetic variants. Primers were designed using the Primer 3.0 software (http://www.genome.wi.mit.edu/cgi-bin/primer/primer3.cgi). After PCR amplification, products were purified (Multiscreen, Millipore) and sequencing was performed using BigDye Terminator (version 2.0) and analyzed on ABI 3730XL sequencers (Applied Biosystems, Foster City, CA). Sequences were then assembled and analyzed using STADEN preGAP4 and GAP4 programs [24]. Sequence screening was performed on DNA from 30 unrelated women from QFS, 15 displaying very low (scores 0–3) and 15 with very high (scores 11–16) levels of disinhibition. Genetic variants were subsequently genotyped on the entire cohort using direct sequencing, as described above.

The Tagger function of the Haploview software, version 4.2 (http://www.broad.mit.edu/mpg/haploview/) was used to compute the linkage disequilibrium (LD; r^2) between the *OR7D4* SNPs with minor allele frequency (MAF) ≥ to 5% (data not shown). These SNPs captured 100% of the genetic variation of *OR7D4*.

Besides *OR7D4*, six other OR genes are located in the 19p13 chromosomal region where we previously found evidence of linkage with disinhibition: *OR1M1*, *OR7G2*, *OR7G1*, *OR7G3*, *OR7D2* and *OR7E24*. These genes may also have an impact on eating behaviors and could be responsible for the linkage evidence previously reported for disinhibition. To test this hypothesis, we analyzed 100 additional SNPs spanning a 162 kb region of chromosome 19p13 including the seven OR genes. These 100 additional SNPs were either derived from a genome-wide association study (GWAS) performed in QFS (43 SNPs) or imputed (57 SNPs) using MACH software and HapMap SNPs (release 22) phasing data from CEU population. The genome-wide genotyping was performed using the Illumina Human 610-Quad chip. The chips were scanned on an Illumina BeadArray reader and the BeadStudio genotyping module software was used to call SNP genotypes. Only SNPs passing quality control (QC) filters, excluding SNPs with call rate <95%, minor allele frequency <1% or deviation from Hardy–Weinberg equilibrium ($p<10^{-6}$), were retained for analyses. The call rates for the 43 GWAS SNPs analyzed were ≥99.5%. The following QC filters were applied for SNPs imputation: SNPs with poor quality of imputation ($R^2<0.3$), missing rate over 5%, minor allele frequency (MAF) <1% and/or HW p-value less than 10^{-6} were not retained in the final imputed data set. Except for five SNPs with R^2 values ranging from 0.54 to 0.87, the R^2 values of all imputed SNPs were ≥0.90.

2.4. Statistical analysis

Calculations of allele frequencies and tests of Hardy–Weinberg were performed on founders using PLINK software (version 1.07, http://pngu.mgh.harvard.edu/purcell/plink/) [25]. Measures of linkage disequilibrium between SNPs were determined using Haploview version 4.2 [26].