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Two novel candidate genes identified in adults from the Newfoundland population with addictive tendencies towards food

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ABSTRACT

Food addiction (FA) is a distinguished clinical feature affecting about 5% adults of the general population in Canada. FA contributes to obesity, however, the underlying genes in FA are largely unknown. The aim of the current study was to search for FA candidate genes using an exome sequencing followed by a verification study using the most significantly associated identified genes. From a total of 752 adults, 24 subjects were selected including 8 obese with high and 8 obese with low/zero FA clinical symptom score (FAO, NFO), and 8 healthy controls with normal BMI and low/zero FA symptom score (Ctrl). Exome sequencing was completed in all three groups. The top 100 SNPs identified were categorized into 5 subgroups based on gene functions: addiction (Ad), psychological disorders, energy metabolism and obesity, and cancer, unknown function or with other diseases. In the verification study, the top 19 SNPs in the Addiction subgroup were genotyped in the entire 752 subjects using Sequenom iPLEX Gold genotyping technology. Comparison of NFO with Ctrl, and FAO with NFO, Ctrl and the combined group of NFO + Ctrl revealed 19 SNPs associated with Ad genes including, TIRAP, MMADHC, ERAP1, NTM, MYPN, GRID1, ITPR2, GPSM1, ZCCHC14, TNN, PPARD, CACNA1C, SIM1, and DRD2. Genetic association analysis was performed. The major allele A of rs2511521 located in DRD2 (OR = 3.1(95% CI 1.1–8.2)) and the minor allele T of rs625413 located in TIRAP (OR = 2.5(95% CI 1.1–5.8)) in NFO subjects significantly associated with increased risk of food addiction.

Using a combination of exome sequencing method and a candidate gene association approach two new FA candidate genes are identified. Further study on the rest of the genes in the other four categories will be warranted.

1. Introduction

Over the past 3 decades, the global prevalence of obesity, defined by a body mass index (BMI) of 30 or higher, has increased substantially. By 2019, it is estimated that 55.4% of the Canadian adult population will be categorized as overweight or obese (Twells, Gregory, Reddigan, & Midodzi, 2014). Obesity is a multifactorial disease and the etiology is not completely understood ("Obesity and overweight," 2016). It has been well documented, however, that genetics (Huang et al., 2015; Qi et al., 2012), endocrine function (Roman, Parlee, & Sinal, 2012; Tang-Péronard, Andersen, Jensen, & Heitmann, 2011), behavioral patterns (Farooqi, 2014; Murray, Tulloch, Gold, & Avena, 2014) and environmental determinants (Kershaw, Albrecht, & Carnethon, 2013) play fundamental roles in the development of obesity. Genetic predisposition might be a key factor responsible for the large individual difference in body weight, body fat and other obesity-related aspects (Barsh, Farooqi, & O'Rahilly, 2000; Gesta et al., 2006). Estimates of the heritable variation contributing to obesity range from 30 to 60% in family studies to 60–80% in twin studies (Fawcett et al., 2010; Rankinen et al., 2006). In a previous study, we discovered that chronic compulsive overeating, defined as food addiction by the Yale Food Addiction Scale (YFAS), significantly contributes to the common form of human obesity (Pedram et al., 2013). Additionally, the clinical symptom count of food addiction defined by the YFAS is highly associated with the severity of obesity (Pedram et al., 2013). Furthermore, one study has reported that the prevalence of food addiction in obese individuals seeking weight loss treatment was 15.2%, while in another study, the prevalence of food addiction in obese subjects not seeking weight loss was 25%

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(Davis et al., 2011; Eichen, Lent, Goldbacher, & Foster, 2013). These studies suggest that food addiction with co-morbid obesity may represent an important subgroup of the obese population with a distinctive etiology.

Accumulating evidence has demonstrated the neurobiological and behavioral similarities between food addiction and substance dependence in both human and animal studies (Blumenthal & Gold, 2010; Davis & Carter, 2009; Fortuna, 2012; Smith & Robbins, 2013; von Deneen & Liu, 2012). In animal models, foods high in sugar and fat are particularly associated with addiction-like behavior (Avena, Bocarsly, & Hoebel, 2012, pp. 351–365; Avena, Rada, & Hoebel, 2008, 2009). In human studies, it has also been suggested that the pattern of food intake in food addiction may parallel substance dependence and this phenomenon might share the same neurobiological, behavioral and clinical framework as conventional drug dependence (DiLeone, Taylor, & Picciotto, 2012; Gearhardt et al., 2011; Meule & Kübler, 2012). Data from family, twin, and adoption studies across several drug classes (opioids, cocaine, cannabis, nicotine, alcohol) strongly implicates the role of genetic factor involved in each aspect of addiction development including vulnerability to initiation, continued use, and propensity to become dependent (Li & Burmeister, 2009; Spanagel, 2013; Wang, Yang, Ma, Payne, & Li, 2014). There also exists a genetic overlap between drug and behavioral addictions like gambling (Spanagel, 2013). Studies have discovered many genes that increase the vulnerability in the development of substance dependence (Crabbe, 2002; Kreek, Nielsen, Butelman, & LaForge, 2005; Noble, 2000; Reed, Butelman, Yuferov, Randesi, & Kreek, 2014; Shi et al., 2002; Weiss et al., 2008; Zucker, 2014, pp. 51–69). For instance, twin studies have shown that the heritability of addictions ranges from 39% (hallucinogens) to 72% (cocaine) (Ducci & Goldman, 2012). Importantly, however, the predisposition to addiction may be caused by genetic variants that are common to all addictions and by those specific to a particular addiction (Kreek et al., 2005). However, to the best of our knowledge, there is little information regarding genes associated with an addictive tendency toward food measured by YFAS. A few studies were reported including a genome-wide investigation of food addiction (Cornelis et al., 2016), an evaluation of potential involvements in dopaminergic reward pathways in the brain (Davis et al., 2013) or mu-opioid receptor gene (Davis & Loxton, 2014). Exome sequencing is a powerful genome-wide screening method and is an effective way to discover disease causing mutations and genes. (Kiezun et al., 2012). Candidate gene-based association study is the most common method for discovering the link between complex disease and genes that are suspected to be associated with phenotypes of interest (Zhu & Zhao, 2007).

In the current study which was the first of its kind in the field, we employed a two-stage approach: an exome sequencing technology as a screening stage followed by a genetic association study to discover and verify genes related to food addiction.

2. Ethics statement

This study was approved by the Health Research Ethics Authority (HREA), Memorial University of Newfoundland, St. John's, Canada, with project identification code: #10.33, (latest date of approval: February 10, 2016). All participants provided written and informed consent.

3. Method

3.1. Study sample

The current study was designed and performed in two stages. Stage I, included a genome-wide screening study using a whole-exome sequencing method on selected samples, and stage II was a verification study using a candidate gene association method on the genes related to addiction found in stage I, in the entire study population.

3.1.1. Stage I

A total of 752 subjects in the food addiction study were used for the selection of patients for the exome sequencing study. All the subjects were part of the CODING (Complex Diseases in the Newfoundland population: Environment and Genetics) study and were recruited from the Canadian province of Newfoundland and Labrador (NL) via advertisements, posted flyers, and word of mouth. The inclusion criteria were: 1) age >19 years, 2) born in NL with a family who lived in NL for at least three generations, 3) healthy without serious metabolic, cardiovascular or endocrine diseases, 4) not pregnant at the time of the study (Pedram & Sun, 2014; Pedram et al., 2013). Among the 752 subjects thirty-four subjects (25 females and 9 males) had a very high symptom counts (>or = 5) calculated by the Yale Food Addiction Scale. Subjects with a BMI of 25 kg/m2 or less were excluded (WHO criteria: greater than 25 is classified as overweight; over 30 is classified as obese ("BMI classification," 2016)). After exclusion, 8 overweight/obese females with high symptom counts (FAO), 8 overweight/obese females and 8 healthy normal weight females with low/zero symptom counts (NFO and control respectively) were selected. All subjects in the three groups were matched for age and physical activity. None of the subjects were smokers or alcoholics, nor substance addicted (or taking any medication).

3.1.2. Stage II

This stage contained the entire 752 subjects.

3.2. Anthropometric measurements

Body weight and height were measured after a 12 hour fasting period. Subjects were weighed to the nearest 0.1 (kg) in a standard hospital gown on a platform manual scale balance (Health O Meter, Bridgeview, IL). A fixed stadiometer was used to measure height to the nearest 0.1 (cm). BMI was calculated by dividing participants' weight in kilograms by the square of his/her height in meter (kg/m^2). Subjects were classified as overweight/obese (BMI $\geq$25.00) and normal weight (BMI = 18.5–24.99) based on BMI according to World Health Organization criteria ("BMI classification," 2016).

3.3. Food addiction assessment

Food addiction diagnosis and food addiction symptom counts were calculated according to the YFAS (Gearhardt, Corbin, & Brownell, 2009; Pedram et al., 2013). This questionnaire consists of 25 items that assess eating patterns over the past 12 months. The YFAS translates the Diagnostic and Statistical Manual IV-TR (DSM-IV-TR) substance dependence criteria in relation to eating behavior (including symptoms such as tolerance and withdrawal symptoms, a vulnerability in social activities, difficulties cutting down or controlling substance use, etc.). The scale uses a combination of Likert scale and dichotomous scoring options. The Likert scoring option is used for food addiction symptom counts (for instance tolerance and withdrawal) ranging from 0 to 7 symptoms. The criteria for food addiction were met when three or more symptoms were present within the past 12 months and clinically significant impairment or distress was present (Gearhardt et al., 2009; Gearhardt, White, Masheb, & Grilo, 2013).