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ORIGINAL ARTICLE

Association Between the Brain-derived Neurotrophic Factor Val66Met Polymorphism and Overweight/Obesity in Pediatric Population

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Background. The brain-derived neurotrophic factor (BDNF) rs6265 (G196A; Val66Met) single nucleotide polymorphism has been associated with BMI and obesity in distinct populations, both adult and pediatric, with contradictory results involving either Val or Met as the risk variant.

Aim of the Study. To determine the association between the BDNF Val66Met polymorphism and BMI in Mexican children and adolescents.

Methods. BDNF Val66Met genotyping by restriction fragment length polymorphism and nutritional status characterized by their BMI-for-age z-scores (BAZ) from pediatric volunteers ($n = 498$) were analyzed by Fisher's exact test association analysis. Standardized residuals (R) were used to determine which genotype/allele had the major influence on the significant Fisher's exact test statistic. Odds ratios were analyzed to measure the association between genotype and normal weight (≥ -2 SD $< +1$ SD) and overweight ($\geq +1$ SD, including obesity, Ow + Ob) status with 95% confidence intervals to estimate the precision of the effect as well as 95% credible intervals to obtain the most probable estimate.

Results. Comparisons between GG (Val/Val), GA (Val/Met) and AA (Met/Met) genotypes or Met homozygotes vs. Val carriers (combination of GG and GA genotypes) showed significant differences ($p = 0.034$ and $p = 0.037$, respectively) between normal weight and the combined overweight and obese pediatric subjects. Our data showed that children/adolescents homozygous for the A allele have increased risk of overweight compared to the Val carriers (Bayes OR = 4.2, 95% CI**[1.09−33.1]).

Conclusion. This is the first study showing the significant association between the BDNF rs6265 AA (Met/Met) genotype and overweight/obesity in Mexican pediatric population.

Key Words: BDNF, BMI z-score, Body weight, Overweight, Obesity.

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Introduction

Obesity Epidemic

Obesity is a global increasing epidemic for both children (1) and adults (2) that compromises human well being. The most critical comorbidities related to adipose tissue excess range from rheumatological conditions to type 2 diabetes mellitus, cardiovascular disease, and increased risk of cancer (3). According to the World Health Organization (WHO) (4), overweight and obesity currently affects 1.9 billion adults and 41 million children under the age of five all around the world, accounting as the fifth leading risk for global deaths with at least 2.8 million adults dying each year as a result of these conditions. Up to the past decade, developing countries such as Mexico, China and Thailand have had the most dramatic increase in obesity (5). Recently, it was published that Mexico has the second prevalence of obesity in the adult population with 22 million obese (30%) in addition to the 26 million adults with overweight, while ranking fourth in children (6). The most recent results from the Mexican health and nutritional survey (ENSANUT, 2012) indicate an overall overweight (Ow) or obesity (Ob) prevalence of 28.8% in children <19 years of age (7,8). In the last 24 years, the highest prevalence was observed among children and adolescents living in urban areas and those from the highest socioeconomic level, while the rate of increase was higher in the lowest socioeconomic status (8).

In general, it is assumed that obesity results from a combination of genetic susceptibility, increased availability and consumption of high-energy foods as well as a decreased requirement and performance of physical activity as a consequence of modern life styles (9). Obesity is a complex condition determined by an intricate interplay of genetic and environmental factors (10). Genetic variants are estimated to account for a range between 40−70% of the heritability of BMI (11,12), including single mutations as well as single nucleotide polymorphisms (SNPs) causing from severe impairment in appetite regulation and early-onset overweight to slightly increased BMI or early-onset obesity (11).

BDNF and Obesity

As for genetic susceptibility, known single-gene mutations (13,14) or syndromes (15) may explain only a small fraction (~5%) of childhood-onset obesity. However, as mentioned previously, obesity can mainly be the result of the imbalance between caloric intake and energy expenditure, so by studying the genes involved in appetite regulation we will be able to unravel the essential molecular network involved in obesity.

One such molecule that has been associated with body weight regulation is the brain-derived neurotrophic factor (BDNF). BDNF is a member of the neurotrophin family of small secreted proteins with major roles in central nervous system (CNS) development. Current data from Ensembl shows that BDNF is located at locus 11p14.1, extends over approximately 67 kb, contains 12 exons with 9 functional promoters for tissue and brain-region specificity and originates 19 transcripts by alternative splicing (16). Information about the pro-BDNF proteolytic processing, mature BDNF and its receptors $p75^{NTR}$ and Trkb, respectively, has been thoroughly reviewed elsewhere (14).

Although it is widely expressed among several tissues (17), BDNF is abundant in the CNS (18,19), predominantly in the hippocampus, amygdala, cerebral cortex, and hypothalamus (20−22). BDNF plays a critical role in nervous system development and function (23,24), and particularly, exerts an anorexigenic function in the brain (25). BDNF molecular alterations have been implicated in conditions affecting body weight such as eating disorders (26,27). One of these variations affecting BDNF is the Val66Met single nucleotide polymorphism (G196A; SNP rs6265). In particular, the 66Met (A variant) allele is biologically relevant as it alters the intracellular processing, trafficking and activity-dependent secretion of BDNF (28,29), and has been associated with several clinical traits such as early seizures, bipolar affective disorders, obsessive-compulsive disorders, eating disorders, BMI, and obesity (30).

As with adults (31), studies involving children and adolescents attempting to examine the association between the BDNF rs6265 polymorphism and age-and-sex specific nutritional status characterized by their BMI-for-age z-scores (BAZ) have shown contradictory results. Some of them have found association between this SNP and childhood BAZ at the upper tail of the BMI distribution in children with European ancestry (32), as well as for BMI and obesity in Chinese (33−35), European American (36), and Croatian (37) children; while others reported no association with BMI in Spanish (38), with BAZ in Mexican children (39), and with extreme obesity in German children and adolescents (40).

The BDNF 66Met (A allele) presents greater plausibility of being associated with BMI increase and overweight/obesity, as it is a functional variant that generates subcellular translocation and activity-dependent secretion deficiencies of BDNF which could resemble the BDNF deficiencies associated with obesity (41,42). However, several articles have pointed to the Val66 allele (G variant) as the risk allele associated with BMI or obesity risk (33−35,43), while others point to the Met66 allele (A variant) (37,44,45), and even to the heterozygous genotype AG (37,46). In example, it has been observed in German children that 66Met carriers, although associated with lower BMI, had an increased calorie intake and reported higher carbohydrates and proteins consumption (47), while in Chinese children carriers of the A allele are at increased risk of obesity when moderate to low physical activity levels are reported (45).

At present, association studies involving BDNF rs6265 and BMI in children and adolescents are still scarce and conflicting. Therefore, the aim of this study was to analyze the relationship and determine the association between the