International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Impact Factor (2012): 3.358

Association of Brain-Derived Neurotrophic Factor (*BDNF*) Variant (rs6265) with Overweight/Obesity or Overfatness, and Effect of Physical Activity Levels in Adolescents Population

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Abstract: ***Childhood and adolescents' obesity are worldwide health issue, characterized by various somatic, psychosocial and psychiatric complications, which translates to adult obesity and other related complications. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that mediates feeding habit, food intake, energy metabolism and weight control. A common variant of the BDNF gene (rs6265) has been associated with various forms of eating disorders, influencing body mass index (BMI) and obesity in various populations. Yet, no similar finding was reported on Malaysian adolescents' population to date. The aim of this study was to determine the association between this variant and obesity, and to ascertain the influence of physical activity levels on the variant in 564 Malaysian adolescents of different ethnic background. We genotyped the variant using TaqMan-based allele-specific PCR assay and the result was analysed using SPSS statistical analysis software, in line with levels of physical activity recorded earlier on. Comparison between overweight/obese and lean individuals revealed that rs6265 A risk allele which is also theminor allele was significantly associated with risk for overweight/obese (p<0.001; OR=3.0; 95%-CI=1.49-4.15) and overfatness (p=0.012; OR=1.06; 95%-CI=0.52-1.68) in the study population. We also observed a significant association (p=0.046) between the minor allele and physical activity. This finding is the first of its kind to reveal significant association between the variant mentioned above, physical activities and obesity in multi-ethnic Malaysian adolescents' population which confirmed several findings in other populations***.

Keywords: body fat percentage (BF %); body mass index (BMI); brain-derived neutrophin factor (*BDNF*); Obesity; Physical activity and variant

1. Introduction

It is proven that obesity is associated with various forms of medical complications including cardiovascular diseases, type 2 diabetes mellitus, stroke, dyslipidaemia and some forms of cancer. Childhood obesity enhances predisposition of individuals to the risk of developing obesity at adult age which perhaps lead to further complications with eventual premature death. [**1,**2] Obesity is one of the common life-threatening metabolic syndromes in the world, [3] spreading across children, young adults and middle age adult.[4]The prevalence of obesity is growing at an alarming rate over the years in which the number increases by 100 % in every region of the world between year 1980 and 2008, [5],and the worldwide population of obese raised to about 500 million (12% of the world's population), with higher percentage in western world and United State of America compared to South-East Asia and Africa. [6]

Though the aetiology of this syndrome is not fully understood, [7]but the few known causes of the disease include imbalance of energy intake and energy expenditure over time, resulting from sedentary life style [8]connected to atherogenic diet, in addition to psychological and genetic factors respectively. [7] It was reported that, individuals' genetic makeups that carry common or rare variants in thousands of polymorphic genes that mediate metabolic activity in human body, interact with environmental factors such as physical activities, sedentary life styleand could perhaps be influenced by obesogenic environment. [9&10]

Being a multi-factorial disease [10],genetic variants that have been identified in genes mediating appetite or satiety, intake of food and energy regulation in the body such as Fat mass and obesity associated gene (*FTO*), melanocortin 4 receptor (*MC4R*), brain derive nutrophin factor (*BDNF*) have found to be strongly connected to obesity development. OthersarePeroxisomal proliferator activated receptor gamma gene (*PPARG*), uncoupling protein 2 (*UCP2*),leptin (*Lep*) and Leptin Receptor (*LepR*) to mentioned but few. These and many more were reported to play key role in early onset of obesity in various populations. [11,12& 13]Their possible link with obesity however, was stressed in a genome wide association study (GWAS). [13, 14]

This study was aimed at genotyping rs6265 *BDNF* variant and investigation of possible association of the variant with obesity/overweight and or overfatness in Malaysian adolescent's, as a whole population and when stratified by ethnicity and genders.

2. Materials and Methods

2.1 Study subjects

Total of 782 healthy Malaysian adolescents comprising Malay, Chinese and Indian ethnic groups, from secondary

schools in Kuala Lumpur, Malaysia were recruited. Demographic data and anthropometric measurements were obtained using weighing scale and Omron body fat analyser (Model HBF-356, Omron Health Care Co., Ltd., Kyoto, Japan). Basically, only 564 out of the total subjects had complete demographic and anthropometric data, and so they were considered as the study population (Sample).The research had sufficient power (>0.800) of statistic and adequately big sample size (n=300 needed for this power) to determine significant association. The study was however; approved by the Ethics Committee, Centre of excellent for research value innovation and Entrepreneurship (CERVIE), UCSI University, Malaysia.

All the subjects were recruited voluntarily and demographic information such as age, gender, race, and physical activity levels were obtained using questionnaire. The recruited subjects were categorised as overweight/obese (BMI $\geq$ 85%) and lean (BMI $\leq$ 84%) to which normal and underweight subjects were merged together as lean with respect to body weight status described by [15, 16].The body fat distribution was based on the gender sensitive cut-off values also described by [17].

2.2 DNA extraction and variant genotyping

Using Wizard Genomic DNA Purification Kit (Promega, USA), genomic DNA was extracted from the subject's buccal cells according to manufacturer's instructions. Quantification and quality determination of the extracted genomic DNA were performed using spectrophotometer and agarose gel electrophoresis respectively .Genotyping of variants was done using TaqMan-based allele-specific PCR assay, according to manufacturer's (Applied Biosystem USA) guidelines, and all the reagents used were also procured from applied biosystem.

2.3 Statistical analysis

Data analysis was performed using SPSS(V. 20.0IBM SPSS Inc., Chicago, IL) software. The results for continuous variables such as BMI and BF% are given as means ± standard deviation. The differences between groups were compared using one way analysis of variance (ANOVA) for continuous variables, and by the Chi square (χ^2) analysis for binary/categorical variables including genotypes, overweight/obese, overfatness and normal fat categories respectively. [18] Allele frequencies for each variant were determined using the software mentioned above as described by [19]. The distribution of minor and wild type alleles was tested for Hardy-Weinberg equilibrium usingχ^2 test. Level of significance was set to α=0.05, with 2-tailedp values. The risk of genotype was also measured by means of odds ratio (OR) with 95% confidence interval (95%-CI).

3. Results

Demographic data for the study population, which comprised of 236 (41.8%) and 328 (58.2%)males and females respectively, with mean age of 14.85±1.27 years, was analysed (Table 1).When compared gender wise we found that the respective mean BMI of males was higher than that of females in the whole population as well as in Malay and Chinese ethnic group respectively. Surprisingly, opposite distribution was observed in Indian population wherein female subjects seemed to have higher mean BMI than their male counterpart. On the contrary, females exhibited higher mean BF% compare to male subjects in the total and respective ethnic group populations. Mean values of the two parameters (BMI and BF%) however, were significantly (p<0.050 lower in Chinese compared to other ethnic groups respectively.

Table 1: Demographic data of study population: Mean ± SD of Age, BMI and BF% for males and females subjects of the total and three ethnic groups.

Variables	Total	Chinese	Malay	Indian	p-value
Age	14.85	14.79 ±	14.86	14.91	0.679
Whole	564	205	220	139	
Male	236	094	079	063	
Female	328	111	141	076	
Whole	20.92	19.85 ±	21.51	21.55	**0.001**
Male	**21.11**	**20.40 ±**	**21.72**	21.39	**0.043**
Female	20.79	19.38 ±	21.45	**21.61**	**<0.001**
BF %					
Whole	20.63	18.59 ±	21.43	22.35	**<0.001**
Male	15.88	14.35 ±	15.83	18.24	**<0.001**
Female	**24.04**	**22.18 ±**	**24.57**	**25.76**	**<0.001**

p<0.050 indicate statistically significance difference. Values with ***** means significantly lower in BMI and BF% compared to those with †in the same raw.

3.1 Prevalence of obesity and over fat, in the study population

We noticed that 23.4% of the total population were overweight/obese and 11.7% were over-fat. The frequency of overweight/obese individuals was significantly (p<0.050) lower compared to that of lean subjects. Whereas no significant difference in frequency was observed when compared over-fat individuals in the total population to subjects with normal body fat distribution (Table 2). Upon being stratified by ethnicity, only the Chinese population show significant (p=0.003) lower frequency of overweight/obese compared to the lean subjects. Generally, the Indian population emerged with the highest prevalence of overweight/obese and over-fatness followed by Malay and Chinese ethnic group respectively.

Table 2: Prevalence of obesity and over fat, in the study population based on BMI and BF %

Variables	BMI, n (%)			BF, n (%)		
	Lean	OW/O	p-value	Normal	Over-fat	p-value
Total	432 (76.6)*	132 **(23.4)**†	**0.031**	498 (88.3)*	66 **(11.7)***	0.405
Male	171 (72.5)	65 (27.5)		207 (87.7)	29 (12.3)	
Female	261 (79.6)	67 (20.4)		291 (88.7)	37 (11.3)	
Ethnicity & Gender						
Chinese	179 (87.3)*	26 (12.7)†	0.003	196 (95.6)*	9 (4.4)*	0.174
Male	75 (79.8)	19 (20.2)		88 (93.6)	6 (6.4)	
Female	104 (93.7)	07 (06.3)		108 (97.3)	3 (2.3)	
Malay	160 (72.7)*	60 (23.3)*	0.267	194 (88.2)*	26 (11.8)*	0.535
Male	55 (69.6)	24 (30.4)		70 (88.6)	9 (11.4)	
Female	105 (74.5)	36 (25.5)		124 (87.9)	17 (12.1)	
Indian	93 (66.9)*	46 (33.1)*	0.406	108 (77.7)*	31 (22.3)*	0.574
Male	41 (65.1)	22 (34.9)		49 (77.8)	14 (22.2)	
Female	52 (68.4)	24 (31.6)		69 (77.6)	17 (22.4)	

OW/O stands for Overweight/Obese, P<0.05 indicates significant difference. Values attached to different symbols in the same raw († and *) differed significantly from one another.

3.2 Genotypic and allelic frequency distribution of rs6265 *BDNF* variant

The genotypic and allelic frequencies of the variant were determined by descriptive statistics using SPSS software, whereby allele A seemed to be the minor allele in the variant. Interestingly, this minor allele also happened to be the risk allele in the study population. Minor allelic frequency (MAF)in the total population for A is 0.334. Upon comparison at ethnic level, the frequencies of minor allele A is significantly lower (p<0.050) in Indian population(table 3). The genotypic frequency of the variants in the study population was in agreement with Hardy-Weinberg equilibrium (HWE).

Table 3: Genotypic and allelic frequency distribution of rs6265 *BDNF* variants for the total population and three ethnic groups.

Genotypic frequency				
Ethnicity/ Genotype	rs6265 (G>A)			
	GG	GA	AA	Total
Chinese	103(50.2)	57 (27.8)	45 (22.0)	205
Malay	89 (40.5)	82 (27.3)	49 (22.3)	220
India	75 (54.0)	38 (27.3)	49 (22.3)	139
Total	267(47.3)	217(38.5)	**80 (14.2)**	564
Male	114 (48.3)	79 (33.5)	43 (18.2)	236
Female	163 (49.7)	97 (29.6)	68 (20.7)	328
Allelic frequency (%)				
Ethnicity/Allele	rs6265 (G>A)			
	G	A	Total	
Chinese	263 (64.2)	147 (35.8)*	410	
Malay	260 (59.1)	180 (40.9)*	436	
India	188 (67.6)	90 **(32.4)**†	278	
Total	751 (66.6)	377**(33.4)**	1128	
Male	307 (65.0)	165 (35.0)	472	
Female	423 (56.5)	233 (35.5)	656	
p-value		<0.050		

P<0.05 indicates significant difference. Values attached to different symbols in the same column († and *) differed significantly from one another.

3.3 Association of rs6265 (G>A) variant with overweight/obese or over-fatness

In the total study population, significantly higher number of subjects with A minor allele of rs6265 variant were overweight/obese (p<0.001, OR: 3.07, CI: 1.49-4.15) and over-fat (p=0.012, OR: 1.06, CI: 0.40-1.53) compared to subjects with homozygous wild type GG genotype which were mostly in the lean/normal body fat category. When stratified according to genders, only females with A minor allele showed significant association with overweight/obesity (p=0.013, OR: 1.06, CI: 0.52-1.68) and over-fatness (p=0.049, OR: 1.57, CI: 0.72-2.58), whereas male subjects who are carriers of A minor allele exhibited

marginal association with over-fatness (p=0.050) as shown in table 4.

When analysed by ethnicity, Malay subjects with A minor allele irrespective of genders were significantly associated with overweight/obesity (p<0.001) and over-fatness (p<0.001), the same trend of association was observed with over-fatness in Malay male subjects (p=0.041). Interestingly, in additive model (GA+AA), the A minor allele was significantly associated with overweight/obese(p<0.001)and over-fatness (p<0.001) in Indian subjects, irrespective of genders.

Table 4: Association of minor allele in rs6265 variant, with overweight/obese and over-fatness phenotypes according to total population, ethnic groups and genders.

			rs6265 *BDNF*				
	Subjects	Status of obesity	GG, n (%)	GA+AA	p-value	OR	CI
BMI (kg/m^2)	**Total**	Lean	227(52.6)	205(47.5)	**<0.001**	**3.07**	**1.49-4.15**
		Overweight/obese	035(26.5)	097(73.5)	**0.013**	**1.06**	**0.52-1.68**
	Female	Lean	129(49.4)	132(50.6)			
		Overweight/obese	030(44.7)	036(53.7)			
	Malay	Lean	069 (43.1)	091 (56.9)	**<0.001**	1.11	0.42-1.93
		Overweight/obese	020 (33.3)	040 (66.7)			
	Male	Lean	023 (41.2)	032 (58.8)	**<0.001**	2.16	1.11-2.81
		Overweight/obese	006 (25.0)	018 (75.0)			
	Female	Lean	049 (46.7)	056 (53.3)	**0.001**	1.58	0.72-2.11
		Overweight/obese	013 (36.1)	023 (63.9)			
	Indian	Lean	065 (63.1)	038 (36.9)	**<0.001**	4.45	3.63-6.31
		Overweight/obese	010 (27.8)	026 (72.2)			
	Male	Lean	022 (53.7)	019 (46.3)	**0.043**	1.67	1.02-2.71
		Overweight/obese	009 (40.9)	013 (59.1)			
	Female	Lean	025 (48.1)	026 (51.0)	**0.002**	1.14	1.31-1.93
		Overweight/obese	011 (54.2)	013 (54.2)			
BF %	**Total**	Normal	229 (48.1)	266 (51.4)	**0.012**	1.06	0.40-1.53
		Over-fat	035 (42.5)	043 (57.5)			
	Male	Normal	098 (47.3)	109 (52.7)	**0.050**	1.11	0.44-1.93
		Over-fat	013 (44.8)	016 (55.2)			
	Female	Normal	142 (48.8)	149 (51.2)	**0.049**	1.57	0.72-2.58
		Over-fat	014 (37.8)	023 (62.2)			
	Malay	Normal	075 (40.8)	109 (49.2)	**<0.001**	1.55	0.49-2.20
		Over-fat	014 (38.9)	014 (53.9)			
	Male	Normal	031 (44.3)	040 (57.1)	**0.041**	1.11	0.42-1.93
		Over-fat	003 (33.3)	006 (66.7)			
	Indian	Normal	057 (52.8)	051 (47.2)	**<0.001**	1.55	0.51-1.94
		Over-fat	013 (41.9)	018 (58.1)			
	Male	Normal	026 (53.1)	023 (46.9)	**0.049**	1.51	0.44-1.97
		Over-fat	006 (42.9)	008 (57.2)			
	Female	Normal	031 (52.5)	028 (47.5)	**0.040**	2.03	0.72-2.66
		Over-fat	006 (35.3)	011 (64.7)			

P-values<0.050 indicate significant association, where increase in Odd Ratio value (OR ≥ 1) signifies effect of the variant on obesity phenotype development.

3.4 Effect of physical activity on BMI and BF% with respect to genotypes of the study variant, analysed using dominant model

Statistically significant differences in Mean BMI (p<0.001) and BF% (p=0.002) were observed between active and inactive males who are carriers of the A minor allele of rs6265 Figure 1(a & b). Meanwhile, the difference between the two categories with respect to the homozygous wild type genotype was not pronounce (p>0.050).

The data however, presented as average mean of BMI and BF% according to number of each group as seen in the figures below.

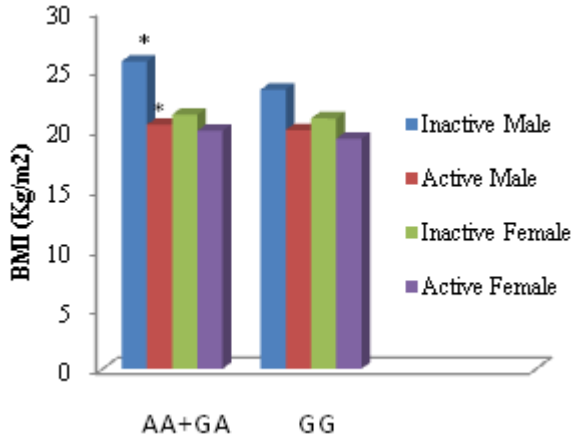

Figure 1(a): Effect of physical activity on BMI in Malaysian adolescents', analysed using dominant model of rs6265 BDNF variant's genotypes with respect to genders

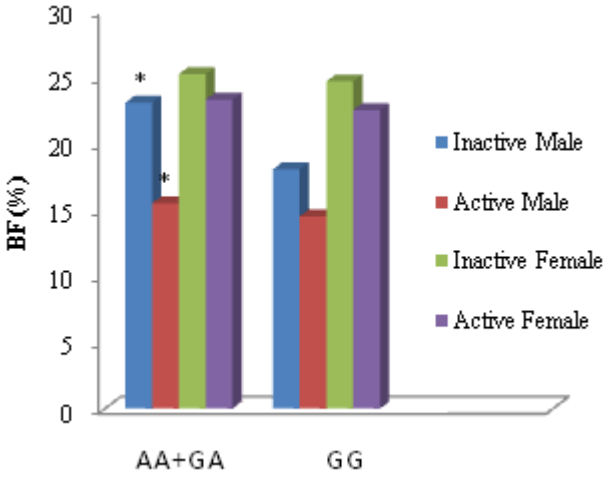

Figure 1 (b): Effect of physical activity on BF% in Malaysian adolescents', analyzed using dominant model of rs6265 BDNF variant's genotypes with respect to genders

It is obvious that, despite carrying the minor allele which is also the risk allele in the variant, those that are physically active (especially males) have significant lower BMI and BF % values compared to the inactive ones among them. This is an indication of the existence of variant physical activity (V-PA) interaction as observed by Scott and his colleagues in Greek adolescents [20], where the variant effect was found to be more pronounced in inactive than active males. The finding clearly highlighted physical activity as an important environmental factor capable of modifying the effect of variants in a given population.

4. Discussion

We have investigated the association of rs6265 variant with obesity phenotype in heterogeneous adolescent population, and compared the allele frequency in our study population to see whether it would match to those of various populations within Asia, Africa and perhaps Europe. Herein, we reported that the minor (Risk) allele in our study population was also the minor allele reported in various population studies including Japanese [8], Belgian women [21], Caucasian children [22], Chinese children [23] and Boston Puerto Rican [24] with respect to obesity development. We also reported the comparison of MAF in our study population to those found in HapMap project international (Data not shown). Where we observed similarities among the MAFs from two sources of nearly the same ancestry, to which we envisage that populations with slightly different MAFs may have virtually common ancestral origin.

This study highlighted the association between minor allele (A) in rs6265*BDNF*variant and morbid obesity indices (BMI and BF%) in Malaysian adolescents of three major ethnic background which include Malay, Chinese and Indian. Herein, significant higher values than normal of both BMI and BF% in those with the minor allele were observed, except in the respective Malay females and Chinese population, in which the result was contrary to what was obtainable in one of the previous studies. [25]Interestingly, the minor allele was found to be associated with overweight-obese or over-fatness in the total population even when stratified to ethnic and gender. This is in line with what was reported in Belgium females, Caucasian children and adolescents as well as Boston Puerto Rican Males population respectively. [21, 22 & 23]*BDNF* play crucial role in regulating energy metabolism and feeding habit [26]. As a neurotrophin, the factor enhances differentiation of neurons, survival during early stage of development, adult neurogenesis and neural plasticity, as such *BDNF* has the potential to modify important circuits' involved in eating behaviour and energy expenditure. [26]

Relative expression of *BDNF* is associated with signalling phosphorylation of AMP-activated protein kinase (AMPK) and acetyl-coA carboxylase beta (ACCβ) as well as increase level of fatty acid oxidation. AMPK sense a high-energy state in muscles and when activated, it phosphorylates the mitochondrial ACCβ, thereby inhibiting increase level of malonyl-coA and increase mitochondrial fatty acids transport and oxidation thus regulating energy metabolism and feeding behaviour. [26]Substitution of G by A nucleotide that occur at position 14.1 on the coding region of *BDNF* gene, result in the change of Alanine to Valine amino acids with subsequent conformational change in the structural protein produced by the gene, thereby affecting the normal function of the factor. [27]

Identification of the minor allele in rs6265 *BDNF* that hinders it from normal function in a given set of population could tremendously help in conceptualising modern personalised medicine and improve the nutritional aspect of life of such population, which in a way provide alternative therapy for obesity and perhaps eating disorders.

This variant was also analysed with respect to level of physical activities (PA) in the study population. Whereby significant association between the minor allele (A) based on BMI/BF% and levels of activity was recorded. The effect of PA was therefore pronounced on the carriers (especially males) of the minor allele of rs6265 variant who engaged themselves in vigorous activity. This is seen when the genotypes of inactive and active females were analysed with respect to obesity indices (BMI and BF%).

Researchers gathered and meta-analysed data from 45 different studies in adults and 9 studies in children. [28] The result showed that the carriers of such variants had 23%

higher risk of developing obesity than those with wild type alleles. But nevertheless, vigorous physical activity lowered the risk. The active adult carriers of variants had about 30% lower risk of obesity than the inactive carriers of the variants. Thus, our finding is in support of the idea that says certain genetic effects may be operating most strongly on groups in a particular environmental condition, and strongly acts on physically inactive subgroups to the pre-adult life stages.

The results also hinted that the studied variant (rs6265) modulate the association of adiposity with physical activity as revealed by the genotype/activity association shown in figure1 above. Despite the fact that the relationship between increasing physical activity and decreasing obesity was ambiguous as reported by [29], high physical activity seemed to play important role in attaining a negative energy balance by speeding up energy expenditure. [30] This could be a good way of getting rid of excess calories, thereby supressing the effect of variants involved in early onset of obesity, enhanced by obesogenic environment.

5. Conclusion

This study is the first of its kind to reveal the associations of rs6265 variant with BMI, BF%, and risk of obesity development in heterogeneous Malaysian adolescents' population comprising Malay, Chinese and Indian ethnic groups respectively. It is important to unveil the impact of genetic susceptibility by investigating the association of genetic variants on obesity candidate genes and adiposity in adolescents. Childhood obesity has higher likelihood of translating to adult obesity in contribution of obesogenic environment. In this study we genotyped rs6265 variant and found that the genotypic and allelic frequencies of the study variants are slightly similar to that of some Asian and European population respectively. We also found out thatrs6265 variant is associated with obesity development at early stage of life. It has also come to our knowledge that physical activity attenuates the effect of this variant in the study population by observing significant higher mean BMI and BF% in the inactive subjects who are carriers of minor allele of the variant. Having clear understanding of the genetic contributions to obesity development especially interactions of genes with environment would provide better understanding of the pathways that lead to adiposity and obesity eventually. This could perhaps give rise to promising strategies by which the morbidity will be prevented and treated well after the onset.

6. Future Study

Future research will focus on the association of this variant with morbid obesity in Malaysian adults of different ethnic background to ascertain the general findings of this study.

7. Acknowledgments

Our sincere appreciation goes to Fundamental Research Scheme of the Ministry of Higher Education (MOHE) Malaysia who funded the research as well as Centre of Excellent for Research, Value, Innovation and Entrepreneurship (CERVIE), UCSI University Malaysia, for their tremendous support.

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