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Association of the BDNF rs6265 variant with obesity in adults from Lahore, Pakistan, and its molecular docking analysis with the TrkB receptor

Faheem Mustafa[1,2], Wajiha Kanwal[3], Rabiatul Adawiyah Umar[1], Mouvez Zeeshan[4], Atif Amin Baig[5] and Wan Rohani Wan Taib[1,*]

[1]*Faculty of Health Sciences, Universiti Sultan Zainal Abidin, Gong Badak Campus, 21300, Kuala Nerus, Terengganu, Malaysia.*
[2]*Department of Nutrition and Dietetics, School of Health Sciences, University of Management and Technology, 54782, Lahore, Pakistan.*
[3]*Punjab AIDS Control Program, Primary and Secondary Healthcare Department, 54000, Lahore, Pakistan.*
[4]*Department of Biomedical Laboratory Sciences, School of Health Sciences, University of Management and Technology, 54782, Lahore, Pakistan.*
[5]*International Medical School, Management & Science University, 40100, Malaysia.*

**Correspondence: wanrohani@unisza.edu.my*

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ABSTRACT

A rapid increase in obesity prevalence has been observed in Pakistan. Multiple genetic and environmental factors disrupt energy homeostasis and increase body weight. BDNF regulates energy homeostasis, body mass index, and lipid parameters. Polymorphism of *BDNF* Val66Met rs6265 can disrupt energy homeostasis and alter BMI and lipid parameters. The primary goal of this study was to investigate the association of *BDNF* rs6265 with anthropometric and lipid profiles in obese Pakistani subjects and to evaluate the binding affinity of wild and mutant BDNF protein with tropomyosin receptor kinase B (TrkB). This case-control study was conducted in the Pakistani population aged 20-59 years. A total of 66 obese and 66 control subjects were included. A total of 2 ml whole peripheral blood was collected. Genotyping analysis of variation in *BDNF* (rs6265) was determined by using PCR-RFLP. *In-silico* analysis of wild and mutant BDNF protein and TrkB was blind-docked with ClusPro. SPSS was used for the statistical analysis. Obese attributes had significantly greater neck circumference, body fat percentage, and lower high-density lipoprotein, as compared to healthy individuals ($P<0.05$). A significant association was observed between genotypic variation rs6265 and hip circumference, waist circumference, BMI, body fat percentage, and cholesterol ($P<0.05$). The AA genotype in obese subjects had the highest count contributing 56% of the obese samples, followed by GG, having a frequency of 44%. There was also a significant difference in both allelic and genotypic frequencies between the obese and normal subjects ($P<0.05$). *BDNF* rs6265 genotypes showed a significant association between obesity and its attributes. Docking results showed that the rs6265 polymorphism in *BDNF* reduced the binding affinity between BDNF and TrkB. These findings highlight the complex role of genetic factors in obesity and suggest that future studies may help inform personalized treatment approaches.

Keywords: *Obesity; BDNF; lipid profile; anthropometric measurements and BMI*

INTRODUCTION

Obesity is an abnormal accumulation of fat in the body, and it is measured by body mass index (BMI) equal to or above 25 kg/m^2 for the Asian population (Jih et al., 2014). Being overweight and obese are the main risk factors for increasing morbidity and mortality, and these are significant health problems and the leading cause of metabolic disorders like diabetes, hypertension, and cardiovascular diseases (Jakobsen et al., 2018; Mustafa et al., 2022).

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Obesity prevalence is increasing rapidly in Pakistan. According to a WHO report, in 2016, 20.8% population was overweight, and 4.8% was obese in Pakistan (Hasan & Hasan, 2017). Obesity results from an imbalance in energy homeostasis. The central nervous system, mainly the hypothalamus, plays a crucial role in energy homeostasis (Myers & Olson, 2012). For a long time, it has been considered that increased caloric intake and physical activity reduction lead to overweight and obesity (Friedman, 2004). However, multiple genetic and environmental factors disrupt energy homeostasis and ultimately increase body weight.

Genetics plays a significant role in determining body weight, and numerous studies have identified over 60 genes associated with obesity (Rosas-Vargas et al., 2011; Yamamoto et al., 1996). Among these genes, 32 are more prevalent and contribute to variations in weight gain among individuals (Rosas-Vargas et al., 2011). However, these genes only increase susceptibility to obesity and require the presence of environmental factors for the disease to manifest (Ernfors et al., 1990). While genetic risk alleles may contribute to some extent to weight gain, the exponential increase in obesity is influenced by various other factors and their interactions (Leibrock et al., 1989). Studies have investigated the interplay between genetic predispositions and environmental exposures such as diet, exercise, and lifestyle. Some genes, known as "Thrifty genes," increase the likelihood of disease onset (Leibrock et al., 1989). For example, a variation in the *FTO* has been linked to a higher risk of weight problems. However, lifestyle and environmental factors account for the majority of the contribution, estimated to be around 77% (Hofer et al., 1990). Although research has primarily focused on a limited number of genetic risk loci and environmental elements, it raises important questions about integrating this complexity into public health and personalized medicine. One gene of interest in this context is the brain-derived neurotrophic factor (*BDNF*), which may have implications for understanding the genetic basis of obesity.

It has been observed that brain-derived neurotrophic factor (*BDNF*) has an important role in controlling energy homeostasis and dietary intake (Ameroso et al., 2022; Lim et al., 2020). Brain-derived neurotrophic factor (BDNF) belongs to the neurotrophin family, and its expression takes place in the nervous system. *BDNF* is located at chromosome 11p14.1 in humans. It has a role in neuronal growth and survival (Sim et al., 2010). It also facilitates the regulation of both energy intake and expenditure. Mechanistically, *BDNF* regulates the leptin-proopiomelanocortin pathway that regulates energy homeostasis, BMI, and lipid parameters. BDNF is released from hypothalamic neurons and can interact with TrkB receptors present on proopiomelanocortin (POMC) neurons. Activation of the BDNF-TrkB pathway in POMC neurons promotes their survival, enhances synaptic connectivity, and stimulates the release of α-melanocyte-stimulating hormone (α-MSH). This, in turn, leads to increased energy expenditure, reduced appetite, and weight loss. Polymorphism of *BDNF* Val66Met rs6265 can disrupt energy homeostasis and alter BMI and lipid parameters (Akkermann et al., 2011; Gratacòs et al., 2007). Hyperphagia and obesity were observed in *BDNF* heterozygous mice (Kernie et al., 2000; Lyons et al., 1999).

Tropomyosin receptor kinase B (TrkB) is activated by BDNF protein, which triggers the BDNF-TrkB signaling pathways and regulates body weight and glucose metabolism (Javed et al., 2023; B. Podyma et al., 2021). It has been shown that BDNF-TrkB signaling is affected by *BDNF* rs6265, leading to alterations in energy balance and metabolism. BDNF is involved in neural activity induced by leptin in the hypothalamus. Dysfunction in the BDNF-TrkB signaling can disrupt neural activity in the hypothalamus and lead to altered energy homeostasis, and obesity (Wu et al., 2025).

However, there has been limited research conducted on the genetic and allelic frequencies of *BDNF* (brain-derived neurotrophic factor) variations and their relationship to obesity in the Pakistani population, as well as the impact of the V66M variant of *BDNF* on the interaction between BDNF and the TrkB receptor, which has been associated with obesity.

The primary study goal was to find the association of *BDNF* variation with anthropometric and lipid profiles in Pakistani obese subjects and evaluate the affinity binding of wild and mutant BDNF protein with tropomyosin receptor kinase B (TrkB) via molecular docking. Preceding genotyping analysis, an *in-silico* analysis assessed the impact of wild-type and mutant BDNF proteins on TrkB interaction. Utilizing these findings, the study investigated the relationship between *BDNF* variations and anthropometric and lipid profiles in Pakistani obese subjects.

METHODOLOGY

Ethical approval was obtained from the UniSZA Human Research Ethics Committee (UHREC) on August 04, 2022, with the reference number: UniSZA/UHREC/2022/388 and from the Office of Research Innovation and Commercialization (ORIC), University of Management and Technology, Lahore, Pakistan on August 08, 2021, with reference number: RE-009-2021 and research was conducted based on the guidelines of the Declaration of Helsinki.

A cross-sectional study was performed among volunteers in the Pakistani population. A total of 66 obese and 66 control subjects having a BMI >25 kg/m² (for obese) and 18.5-22.9 kg/m² (for normal healthy individuals) (Jih et al., 2014) aged 20-59 years were included through convenience sampling method. Participants with any metabolic and inflammatory diseases, or those taking any medication were not included. PS (Power and Sample Size Calculator), version 3.1.2, was used to calculate the sample size. Table 1 shows the output details of PS software.

Table 1

Details used for sample size calculation through PS software

Type	Values
Study Type	Dichotomous
Requested Table output	Sample size The Alternative hypothesis showed two proportions
Level of significance, alpha (α)	0.05
Power of study (1-β)	0.84
Po(control)	0.44 (Mustafa et al., 2022)
P1 (experimental)	0.17 (Mustafa et al., 2022)

Note: m: the ratio of obese to non-obese individuals. Here, the ratio was set as 1, α: Level of significance, β: the power of the study

The sample size calculated through PS software was 50 to be taken for each group (obese and normal). For a 20% estimation of missing data, 60 samples were needed. The sample size was increased to 66 subjects per group. The inclusion and exclusion criteria of subjects are shown in Table 2.

Table 2

Inclusion and exclusion criteria of the sample

Selection of Obese Individuals		**Selection of Normal Individuals**
Inclusion Criteria	**Exclusion Criteria**	**Healthy individuals**
66 individuals with a BMI 25 kg/m^2 or above and age 20-60 years	Presence of metabolic and inflammatory diseases	66 Individuals with BMI 18.5-22.9 kg/m^2 and age 20-60 years
Without any other medical diagnosis	Individuals taking any medication	

Anthropometric measurements

Anthropometric data of participants were taken with thin clothes and naked feet. Weight was measured in kilograms (kg) by using the weight machine, and height in centimeters (cm) by using a stadiometer. The standard formula, i.e., weight (kg)/height (m^2), was used to calculate the BMI (body mass index) (Mustafa et al., 2022). Waist circumference was measured by measuring tape between the bottom of ribs and iliac crest after breath out. A measuring tape was also used to measure the hip circumference around the widest part of the hip. The US Navy method was used to calculate the fat percentage of the body (Malvi et al., 2022; Peterson, 2015).

Collection and preparation of whole blood sample

A total of 4 ml of the fasting whole blood sample was collected from the median cubital vein in the EDTA-containing blood collection tube by the phlebotomist (2ml was used for DNA extraction and remaining 2ml was used for lipid profile analysis). Blood sample was centrifuged to separate serum. The serum was stored at 2-8°C to analyze the lipid profile and DNA extraction within two weeks of being drawn.

Lipid profile

Lipid profile analysis was conducted using an enzymatic calorimetric method (Roche Diagnostics) (Suchánek et al., 2009). Instruments such as a spectrophotometer were used to measure the absorbance of reaction products formed during enzymatic reactions, facilitating the quantification of lipid components. Additionally, a chemistry analyzer, along with a centrifuge for serum isolation, enabled precise analysis and quantification of lipid components. A standard pipetting system was utilized for reagent and sample dispensing, ensuring accuracy throughout the analysis.

Genotypic analysis of *BDNF* rs6265

The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to determine the genotypic and allelic frequencies of *BDNF* gene (rs6265) polymorphism using a set of primers and evaluate the association of the SNP with obesity as exhibited in Table 3.

Table 3

Primers used for genotyping of variation in the exonic region of BDNF (rs6265) variation

Primer used	Sequence	Melting temperature	Reference
For *BDNF* (rs6265)			
Forward	5'- ACTCTGGAGAGCGTGAAT -3'	54°C	(Sim et al., 2010)
Reverse	5'-ATACTGTCACACACGCTC-3'	54°C	

The master mix solution was prepared for the amplification of variation in the exonic region of the *BDNF* (rs6265). The conditions for the polymerase chain reaction (PCR) were optimized for both sets of primers. The restriction analysis of the PCR-amplified products of *BDNF* (rs6265) was performed. Restriction enzyme was selected after analyzing through Vector NTI Advance® 9.0 software (Lu & Moriyama, 2004). Restriction analysis of PCR amplified product of *BDNF* was performed by *NLAIII* restriction enzyme with the restriction site CATG.

Computational evaluation of BDNF protein with tropomyosin receptor kinase B (TrkB)

Molecular docking by using the Cluspro online server

For computational evaluation of BDNF protein with tropomyosin receptor kinase B (TrkB), the BDNF structure was downloaded from the Alpha Fold Database with Accession ID: Q6YNR1. The Tropomyosin receptor kinase B (TrkB) structure was also downloaded from Alpha Fold with Accession ID: W8VY28. The BDNF mutant structure was created on PyMOL by changing the amino acid number 66 from Valine to Methionine. The cluster server was used to perform molecular docking to analyze the effect of mutation on the binding affinity of the BDNF with the TrkB protein (Kozakov et al., 2017).

Visualization of docking complexes by using the PDBsum online server

The PDBsum online server (http://www.ebi.ac.uk/thornton-srv/databases/pdbsum Generate) was used to visualize the interaction network that investigated the interaction result, i.e., salt bridge, non-bonded contact, along with hydrogen bond and the interacting amino acids residues were labeled by using PyMOL software.

Statistical and data analysis

Statistical and data analysis was performed for the objectives and analysis of the specific outcomes. Statistical Package for Social Sciences (SPSS), version 22.0 (IBM Corporation, Armonk, NY) was used for the statistical analysis. Shapiro-Wilk normality test was used to confirm that the data follows a normal distribution. For the continuous variables, means and standard deviations were used, while for the categorical variables, percentages and frequencies were used. The chi-squared (χ^2) test of independence was performed for the bivariate association between the categorical variables. The association between continuous variables was analyzed through Pearson's correlation test. Moreover, sample demographics and the genotypes of variation in the exonic region of *BDNF* (rs6265) were explored through chi-square (χ^2) and independent-samples *t*-test.

RESULTS

Demographic distribution

The gender distribution analysis provides insights into the association between gender and obesity among the subjects. A total of 132 subjects were included in the study. Among them, 78 individuals accounting for 59% of the subjects were men, while 54 individuals representing 40.9% of the subjects were women. Within the men group, 57.69% were classified as obese, while 42.3% were categorized as normal weight. In contrast, within the women group, 38.8% were classified as obese, while a larger proportion, 61.1% were considered to have a normal weight. These results indicated that the prevalence of obesity was higher among men (57.69%) compared to women (38.8%). This gender disparity in obesity prevalence suggests a potential association between gender and weight status within the studied population.

The age distribution analysis showed the association between age and obesity among the subjects. The study included a total of 132 subjects, with their ages distributed across various categories. The majority of the subjects, 75% of the total subjects, fell into the age range of 20-30.9 years. There were 99 individuals within this age group. The next age category, comprising 18.9% of the subjects, was 31-40.9 years, with 25 individuals. The age range of 41-49.9 years accounted for 4% of the subjects, with 6 individuals falling into this category. Lastly, individuals aged 50 years or older represented 1.5% of the subjects, with 2 subjects in this age group.

In the obese category, 77.2% of the subjects were found to be between the ages of 20-30.9 years, indicating a higher prevalence of obesity within this age range. The proportion of obese subjects decreased in older age groups, with 13.6% falling into the 31-40.9 years range, 6% in the 41-49.9 years range, and 3% in the ≥50 years category. Conversely, within the normal weight category, the highest percentage of subjects, 72.7%, were found in the 20-30.9 years age range. This proportion decreased slightly to 24.2% in the 31-40.9 years range and 3% in the 41-49.9 years range. Overall, the results indicated that the highest prevalence of obesity was observed among subjects aged 20-30.9 years. This suggests a potential association between age and the occurrence of obesity within the studied population. Table 6 shows the gender and age classification in the present study.

Anthropometric indices of subjects

The results of the anthropometric indices analysis provide insights into the differences between obese and normal-weight subjects in terms of weight, hip circumference, neck circumference, body fat percentage, and body mass index (BMI). The means and standard deviations of these anthropometric measurements were determined for both obese and normal-weight subjects. Among the obese subjects, the mean weight was found to be 84.8 kg±12.43681, the mean neck circumference was 37 cm±1.28575, and the mean hip circumference was 99.7 cm±10.25608, while the mean body fat percentage was 28.42. Additionally, the mean BMI among the obese subjects was calculated as 31. On the other hand, among the normal-weight subjects, the mean weight was significantly lower at 57 kg. The mean hip circumference, neck circumference, and body fat percentage were 98.3 cm, 30.68 cm, and 24.65, which was lower compared to the obese group. Furthermore, the mean BMI in the normal weight group was 21.3, indicating a lower average BMI compared to the obese group.

These results indicated that obese subjects had higher mean values for weight, hip circumference, neck circumference, body fat percentage, and BMI compared to the normal-weight subjects. The differences observed in these anthropometric indices suggest that these measurements can serve as indicators of obesity status, with higher values being associated with obesity. Table 6 summarizes the results of anthropometric indices of subjects.

Genotypic characterization of variation in *BDNF* (rs6265) in Pakistani subjects

The region of interest in the exonic region of *BDNF* was amplified through PCR. The restriction analysis was performed after the confirmation of PCR products. Restriction of PCR product (243bp) of *BDNF* resulted in two variants; homozygous variant 66Met (AA) and homozygous wild type 66Val (GG). The existence of the A (66Met) allele was indicated by the presence of 68bp and 175bp DNA fragments, while the existence G (66Val) allele was indicated by the presence of the undigested PCR product (243bp). No heterozygosity was observed among the recruited subjects. Figure 1 shows the genotypic characterization of *BDNF* (rs6265).

Determination of the genotypic frequency of the *BDNF* (rs6265) variation among subjects

The genotype of *BDNF* (rs6265) identification was determined through agarose gel electrophoresis. It was observed that, out of total subjects (n=132), 56.8% (n=75) have GG genotype and 43.2% (n=57) have AA genotype with lacking AG genotype. The genotypic frequency of GG (56.8%) was higher than AA genotype. In obese subjects, GG genotype frequency was 44%, and AA genotype frequency was 56%. However, in normal subjects, the genotype frequency of GG was 70% and AA was 30%. The genotype frequency of AA was found to be higher in obese subjects than in normal and a significant association ($P<0.05$) was observed between *BDNF* rs6265 and obesity. No heterozygous was observed in both non-obese and obese groups. Table 4 summarizes the genotypic frequency of *BDNF* (rs6265) variation. The allelic frequencies are summarized in the following Table 5.

It was found that the frequency of the G allele was 56.8% (n=150), indicating that it was more prevalent in the sample population compared to the A allele, which had a frequency of 43.2%. Furthermore, when examining the association between allelic frequencies and obesity status, it was observed that among the obese subjects, the frequency of the A allele was higher at 56%. In contrast, among the normal-weight subjects, the frequency of the A allele was lower at 30%. These results suggest that the A allele of the *BDNF* variation (rs6265) may be associated with an increased risk of obesity. The higher frequency of the A allele among obese subjects compared to normal weight subjects suggests a potential role of this allele in the development or predisposition to obesity.

Figure 1

Genotypic characterization of variation in BDNF (rs6265) in Pakistani subjects

Lane 1: 100 BP DNA Ladder
Lane 2: Unrestricted PCR Product (GG genotype)
Lane 3: Unrestricted PCR Product (GG genotype)
Lane 4: Unrestricted PCR Product (GG genotype)
Lane 5: Unrestricted PCR Product (GG genotype)
Lane 6: PCR Blank
Lane 7: PCR Blank
Lane 8: **Restricted with NlaIII (AA genotype)**

Table 4

Observed genotypic frequencies of variation in the exonic region of BDNF (rs6265) in Pakistani subjects

Variable	***BDNF* (rs6265)**		Total	P-value
	AA	**GG**		
Normal	20(30%)	46(70%)	66(50%)	**<0.001**
Obese	37(56%)	29(44%)	66(50%)	
Total	57(43.2%)	75(56.8%)	132(100%)	

Note: Significant association at p<0.05, highly significant association at p<0.01

Table 5

Observed allelic frequencies of variation in the exonic region of BDNF (rs6265)

Genotype alleles *BDNF* (rs6265)	**Obese**	**Normal**	**Observed frequency**
G allele	58(44%)	92(70%)	150(56.8%)
A allele	74(56%)	40(30%)	114(43.2%)
Total	132	132	264

Bivariate analysis of BMI and *BDNF* (rs6265)

Bivariate analysis of the body mass index in Pakistani subjects

Independent sample t-test and chi-square were used for bivariate analysis of variables between obese and normal subjects to determine the association for their demographic characterizations, anthropometry, lipid profiles, and genotypic variation. It was observed that the gender of the subjects was significantly associated with BMI, with a p-value less than 0.05. Neck circumference was found to be significantly higher in obese subjects compared to normal-weight subjects, with a p-value less than 0.05. This indicates that neck circumference can serve as an anthropometric parameter associated with obesity in Pakistani adults.

Furthermore, obese subjects had higher fat percentages than normal subjects, with a p-value less than 0.05. This suggests that an increased fat percentage is associated with obesity. Regarding lipid profiles, HDL levels were found to be significantly lower in obese subjects compared to normal subjects, with a p-value less than 0.05. This indicates that low HDL levels are associated with obesity. In addition, a significant association was observed between the genotypic variation of the *BDNF* gene (rs6265) and obesity, with a p-value less than 0.05. However, no significant associations were found between obese subjects and hip circumference, waist circumference, cholesterol, triglycerides, LDL, and VLDL (P>0.05). Table 6 shows the bivariate analysis of BMI.

Bivariate analysis of the *BDNF* (rs6265) variation in Pakistani subjects

The association of genotypic frequencies of variation in the exonic region of *BDNF* (rs6265) with their measured variables (demographic, anthropometric, and lipid profile) was determined through independent sample t-test and chi-square. Regarding demographic characteristics, no significant associations were found between the genotypic frequencies of *BDNF* (rs6265) variation and sex or age (P>0.05). This implies that the distribution of genotypes did not differ significantly based on sex or age. However, significant associations were observed between the genotypes of *BDNF* (rs6265) variation and certain anthropometric measures, specifically hip circumference and waist circumference.

These associations were found to be statistically significant, with p-values less than 0.05.

Furthermore, associations were found between body fat percentage and body mass index (BMI) with the genotypic frequencies of *BDNF* (rs6265) variation (P<0.05). This indicates that different genotypes of *BDNF* (rs6265) may be associated with variations in body fat percentage and BMI among the subjects. In terms of lipid profile indices, the genotypes of *BDNF* (rs6265) variation showed a significant association with cholesterol levels (P<0.05). However, no significant associations were observed with other lipid profile measures such as neck circumference, triglycerides, HDL, LDL, and VLDL (P>0.05). These findings provide evidence for potential associations between the genotypic frequencies of *BDNF* (rs6265) variation and specific anthropometric measures, body fat percentage, BMI, and cholesterol levels. Table 7 shows the bivariate analysis of the *BDNF* (rs6265) variation.

Table 6

Bivariate analysis of the body mass index in Pakistani subjects

Variable	Body Mass Index (BMI)		Test statistic	P-value
	Normal (66)	Obese (66)		
Demographic indices				
Gender			χ^2	**0.002***
Men	33 (42.3%)	45 (57.69%)		
Women	33 (61.1%)	21 (38.8%)		
Age			χ^2	0.164
20-30.9 years	48 (72.7%)	51 (77.2%)		
31-40.9 years	16 (24.2%)	9 (13.6%)		
41-49.9 years	2 (3%)	4 (6%)		
≥ 50 years	0	2 (3%)		
Anthropometric indices Mean (SD)				
Hip circumference	98.8333 (9.36702)	99.7000 (10.25608)	t-test	0.613
Waist circumference	89.2727 (10.36198)	87.5382 (10.73849)	t-test	0.347
Neck circumference	30.6818 (.26982)	37.0000 (.15826)	t-test	**0.006***
BMI	21.3552 (1.27908)	31.0773 (2.88452)		
Fat Percentage out of Total Body	24.6572 (12.22280)	28.4269 (14.18648)	t-test	**0.008***
Lipid profile indices Mean (SD)				
Cholesterol	171.0909 (30.04188)	160.6818 (43.33986)	t-test	0.074
Triglyceride	107.1667 (65.25821)	121.0758 (60.16856)	t test	0.430
HDL	40.3333 (9.26587)	36.1515 (10.51335)	t-test	**0.017***
LDL	101.9545(28.17715)	94.8788 (28.08641)	t-test	0.151
VLDL	22.5758 (14.00776)	22.7576 (11.27292)	t-test	0.495
Genotypic characterization				
BDNF rs6265			χ^2	**<0.001***
AA	20(30%)	37(56%)		
GG	46(70%)	29(44%)		

Note: Significant association at p<0.05, highly significant association at p<0.01

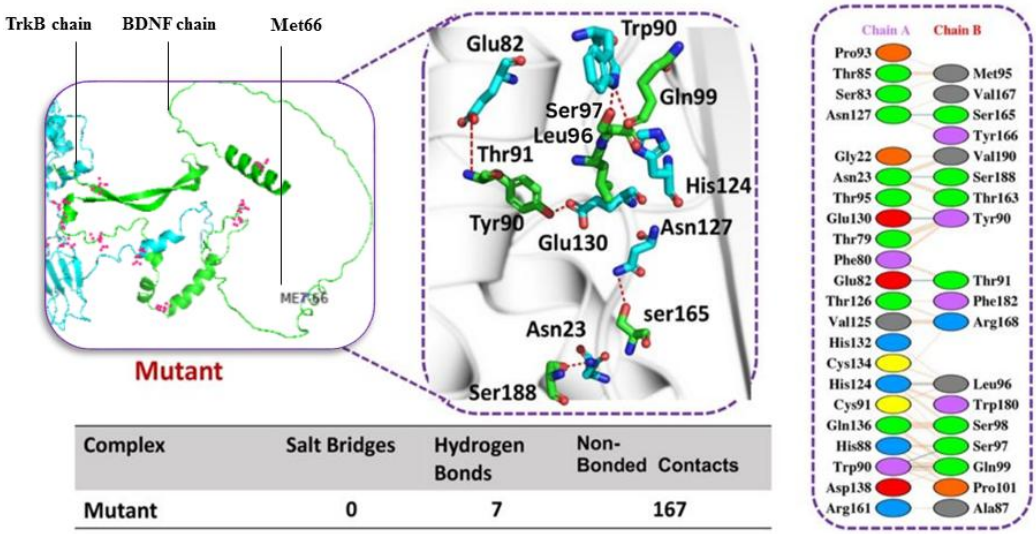
***In-silico* analysis of wild and mutant BDNF protein with Tropomyosin Receptor Kinase B (TrkB)**

The Cluspro server was used to perform the molecular docking of wild-type and mutant BDNF protein with TrkB protein and identify the binding network of wild-type and mutant BDNF protein and the underlying mechanism behind this variation. The predicted docking score for the wild-type BDNF and TrkB protein complex was -1217.5 kcal/mol. The analysis of the interaction interface by the PDBsum online server revealed that the complex between wild-type BDNF

and TrkB protein complex forms three salt bridges, eight hydrogen bonds, and 166 non-bonded contacts. The hydrogen bonds formed between Glu146-Ala29, Lys196-Asp474, Gln159-Asn521, Arg199-His586, Arg168-Ala11, Met95-His8, and Ser165-Arg14 amino acid residues. The salt bridges were formed between Lys196-Asp474, Arg199-Glu590, and Arg154-Asp475 amino acid residues. The stick representation of a binding network of wild-type BDNF and TrkB complex is shown in Figure 2.

Figure 2

Bonding network analysis of wild-type BDNF and TrkB

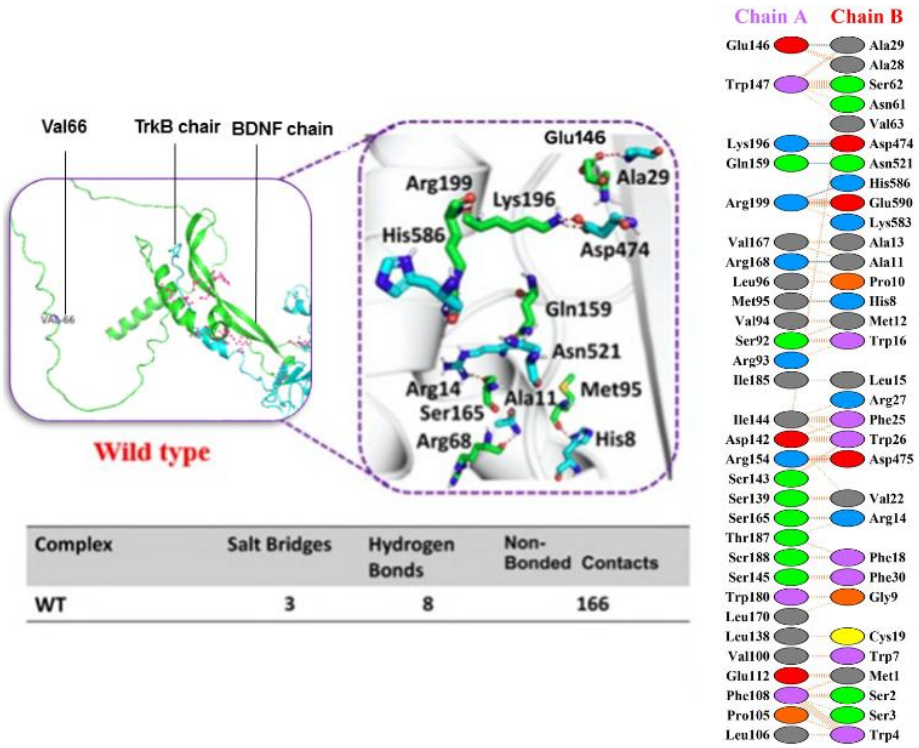


Complex	Salt Bridges	Hydrogen Bonds	Non-Bonded Contacts
Mutant	0	7	167

Note: Figure 2 illustrates the bonding network between wild-type BDNF and the TrkB receptor. The interaction is characterized by 7 hydrogen bonds, 0 salt bridges, and 167 non-bonded contacts

Figure 3

Bonding network analysis of Mutant BDNF and TrkB



Complex	Salt Bridges	Hydrogen Bonds	Non-Bonded Contacts
WT	3	8	166

Note: Figure 3 shows the bonding network between mutant BDNF and the TrkB receptor. Compared with the wild type, the mutant complex forms 8 hydrogen bonds, 3 salt bridges, and 166 non-bonded contacts.

Table 7

Bivariate analysis of the BDNF (rs6265) variation in Pakistani subjects

Variable	*BDNF* (rs6265)		Test statistic	P-value
	AA (57)	GG (75)		
Demographic indices				
Gender			χ^2	0.114
Men	44 (33.3%)	34 (25.7%)		
Women	13 (9.8%)	41 (31%)		
Age			χ^2	0.332
20-30.9 years	39 (29.5%)	60 (45.45%)		
31-40.9 years	14 (10.6%)	11 (8.33%)		
41-49.9 years	2 (1.5%)	4 (3%)		
≥ 50 years	1 (0.75%)	1 (0.75%)		
Anthropometric indices Mean (SD)				
Hip circumference	96.8439 (9.46400)	101.1080 (9.69848)	t-test	**0.018***
Waist circumference	85.3818 (9.53943)	90.7035 (10.75566)	t-test	**0.042***
Neck circumference	34.6667 (3.73847)	33.2933 (3.54802)	t-test	0.985
BMI	27.7769 (5.53137)	24.2357 (5.29450)	t-test	**0.003***
Fat Percentage out of Total Body	21.6006 (11.07472)	30.2975 (13.72681)	t-test	**0.034***
Lipid profile indices Mean (SD)				
Cholesterol	196.2281 (30.04188)	162.4800 (36.63161)	t-test	**0.044***
Triglyceride	113.8246 (54.06383)	114.3467 (60.16856)	t test	0.541
HDL	39.9833 (9.26587)	36.1515 (10.51335)	t-test	0.084
LDL	100.0000 (27.37744)	95.6324 (28.08641)	t-test	0.394
VLDL	24.5758 (13.00776)	22.7576 (12.27292)	t-test	0.481

Note: Significant association at p<0.05, highly significant association at p<0.01

The binding of mutant BDNF with TrkB protein was analyzed to check the effect of mutation on the binding efficiency and compared with the wild type. The docking score for the mutant BDNF-TrkB complex generated by the Cluspro online server was -1211 kcal/mol. The analysis of the interaction interface by the PDBsum online server revealed that the complex between mutant BDNF and TrkB protein complex forms only seven hydrogen bonds and 167 non-bonded contacts. The hydrogen bonds formed between Asn127-Ser165, Asn23-Ser188, Glu130-Tyr90, Glu82-Thr91, His124-Leu96, Trp90-Ser97, and Trp90-Gln99 amino acid residues.

In molecular interactions, energy is released, thereby represented as negative. A lower binding energy (more negative) typically signifies a more stable complex. The results of the present study indicate a decrease in binding energy between mutant BDNF and TrkB in comparison to the wild-type BDNF-TrkB complex. This suggests that the mutation in the BDNF protein has led to a reduction in affinity (-1211 Kcal/mol) between BDNF and TrkB, consequently reducing the binding interactions, including salt bridges and hydrogen bonds. The stick representation of a binding network of mutant BDNF and TrkB complex is shown in Figure 3.

DISCUSSION

Obesity prevalence has been increasing and resulting in high rates of almost all heart diseases and diabetes mellitus. Obesity is known to be a multifactorial disease with a combination of low physical activity, unhealthy diet, lifestyle, and genetics (Chooi et al., 2019). Neurotrophins, including BDNF, play a crucial role in regulating body weight and energy balance. BDNF interacts with two receptors, TrkB and p75NTR, which have opposing effects on appetite and weight gain. TrkB acts as an appetite-suppressing receptor, while p75NTR promotes weight gain and increased food consumption. The factors determining whether BDNF signals through TrkB or p75NTR in metabolic contexts are currently unknown. BDNF is initially secreted as an immature form called proBDNF, which binds exclusively to p75NTR. However, when energy supplies are sufficient or excessive, proBDNF can be cleaved into BDNF, switching the activity from orexigenic to anorexigenic. This suggests that a single cleavage event regulates the switch from p75NTR to TrkB activity, converting proBDNF to BDNF. Further research is needed to understand the precise mechanisms underlying these processes (Brandon Podyma et al., 2021). Polymorphism of *BDNF* Val66Met rs6265 can disrupt energy homeostasis and alter BMI and lipid parameters (Akkermann et al., 2011; Gratacòs et al., 2007). The aim of the study

was to analyze the interaction of BDNF protein with tropomyosin receptor kinase B (TrkB) and to determine the genetic association of variation in the BDNF (rs6265) gene with anthropometric indices and lipid profile in Pakistani subjects.

In this study, it was observed that in men, 57.69% of subjects were obese and 42.3% were normal, while in women, 38.9% of subjects were obese and 61.1% were normal. These findings are consistent with prior research conducted in Multan, Pakistan, suggesting 46% of people were overweight and obese while 24.55% were normal (Choo, 2002).

The present study showed that the means of hip circumference, body fat percentage, and body mass index were 99.7cm±10, 28%±14 and 31±2 in obese subjects, which is higher than the means of hip circumference (98.3cm±9), body fat percentage (24%±12) and body mass index (21.3±1.2) in the normal subjects. The results are consistent with the study conducted in Pakistan reported a higher mean value of BMI in obese (women: 33.89±0.63, men: 32.26±0.69) than normal subjects (women: 22.60±0.63, men: 21.67 ± 0.56) (Qureshi et al., 2006). The observed differences underscored the significance of early intervention and targeted health promotion strategies to mitigate obesity-related risks. However, the mean waist circumference in obese subjects was 87cm±10, which is lower than the mean waist circumference (89cm±10) in normal subjects. The observation of slightly higher waist circumference in normal-weight individuals compared to obese individuals could potentially be influenced by a variety of factors, including body composition, muscle mass, bone structure, and fat distribution patterns. The findings may also be influenced by the study's sample size. Additionally, measurement errors, such as inconsistencies in technique or clothing worn during measurement, could further confound the findings.

The means of triglycerides (121.0758±60.16856 mg/dl) and VLDL (22.7576±11.27292 mg/dl) were higher in obese subjects than normal subjects. However, the mean HDL (40.3333±9.26587 mg/dl) was higher in normal subjects than in obese. These results are in line with the previous studies, which mentioned an increase in triglycerides and a decrease in HDL in the obese group compared with the normal group subjects (Feingold, 2020). These findings suggested the association between lipid profile measurements and obesity.

In the current study, the restriction of the PCR product (243bp) of the *BDNF* resulted in two variants: homozygous 66Met (AA) and homozygous 66Val (GG). To interpret the results and estimate the genotypes of the samples, the presence or absence of specific DNA fragments was considered. The presence of the A (66Met) allele was indicated by the presence of 68bp and 175bp fragments, while the presence of the G (66Val) allele was indicated by the presence of an undigested 243bp fragment. Samples showing the presence of both the 68bp and 175bp fragments were classified as homozygous 66Met (AA) genotypes. On the other hand, samples exhibiting only the 243bp fragment were classified as homozygous 66Val (GG) genotypes.

These findings provide valuable information about the distribution of genotypes in the studied population. The identification of the homozygous genotypes (AA and GG) indicates that the individuals carry two copies of either the A or G allele at the specified locus. This information is important for understanding the genetic variations and potential associations with phenotypic traits or diseases. It was observed that the majority (n=75) of them (56.8%) had the GG genotype, while 43.2% of them (n=52) had the AA genotype ($p<0.001$), suggesting a lack of the heterozygous form (AG genotype). The limited sample size could contribute to the skewed representation, as a smaller sample might not fully capture the complete spectrum of genetic variation within the population, potentially leading to the absence or underrepresentation of certain genotypic forms. Another study conducted in Korea showed that 23.4% of subjects had the AA genotype, 45.9% had GA, and 30.7% had the GG genotype. Similarly, a study in Japan showed that 15% of subjects had AA, 47% had GA, and 38% had GG genotype. A study in China showed that 21% had AA genotype, 48.1% GA, and 30.5% had GG genotype (Imtiaz, 2019).

The present study indicated that there was a significant association between the sex of the subjects and BMI ($P<0.05$). It was found that obesity was more prevalent in males compared to females. This finding aligns with previous research that has shown a higher prevalence of obesity in males (Hashmi et al., 2013). However, it contradicts with findings of a study conducted in Lahore, Pakistan, that showed a high prevalence of obesity in women as compared to men (Mustafa et al., 2022).

Furthermore, a significant association was observed between neck circumference and obesity, with a P value of <0.05. This finding is in line with previous research indicating that neck circumference is a reliable anthropometric measure for assessing obesity (Hatipoglu et al., 2010). Additionally, BMI showed a significant and positive correlation with body fat percentage ($p<0.01$), that in line with the study done in the United Kingdom showed a similar result of a positive correlation between BMI and body fat percentage (Borgeraas et al., 2018).

The study also examined the lipid profiles of the subjects. It was found that obese subjects had lower levels of high-density lipoprotein (HDL) compared to normal subjects, and the difference was statistically significant ($P<0.05$). This result is consistent with previous studies that have consistently demonstrated an inverse relationship between obesity and HDL levels (Tungtrongchitr et al., 2013). Regarding genotypic variation, the study identified a significant association between the *BDNF* (rs6265) genotypic variation (AA, GG) and obesity, with a P value less than 0.05, in line with the previous studies conducted by Beckers et al and Martínez-Ezquerro et al (Beckers et al., 2008; Martínez-Ezquerro et al., 2017). This finding suggests that *BDNF* may play a role in the development of obesity, which is supported by previous research indicating the association of *BDNF* rs6265 with obesity (Ma et al., 2012). However, this finding contradicts with a previous study showed insignificant association of *BDNF* rs6265 with obesity.

Obese subjects were not associated significantly with cholesterol, triglycerides, low-density lipoprotein, and very low-density lipoprotein. These results contradict the previous studies that have shown a positive association between obesity and these lipid parameters (Hertelyova et al., 2016). The small sample size of the study might have limited its statistical power to detect significant associations. Additionally, differences in population characteristics, such as genetic background, lifestyle factors, and dietary habits, could have influenced lipid metabolism and its relationship with obesity.

The study also investigated the association between genotypic frequencies of the *BDNF* (rs6265) variation and various measured variables, including demographic, anthropometric, and lipid profile indices. Independent sample t-tests and chi-square tests were used to analyze the data. The results indicated that there was no significant association between sex and age and the genotypic frequencies of the *BDNF* (rs6265) variation ($P>0.05$). This suggests that the distribution of genotypes did not differ significantly between men and women or across different age groups in the study population. These findings are consistent with previous research that has not shown a significant association between gender or age and the *BDNF* (rs6265) variation (Cunha et al., 2006).

Regarding anthropometric measurements, significant associations were observed between the genotypic frequencies of the *BDNF* (rs6265) variation and hip circumference and waist circumference ($P<0.05$). This indicates that individuals with different genotypes had significantly different mean hip and waist circumference measurements. These findings align with previous studies that have reported associations between the *BDNF* (rs6265) variation and measures of central obesity (Ma et al., 2012). Furthermore, body fat percentage and BMI showed significant association with the genotypic frequencies of the *BDNF* (rs6265) variation that is consistent with the result of previous research indicating a role of BDNF in regulating energy balance and body weight (Miksza et al., 2023).

Regarding lipid profile indices, a significant association was found between the genotypic frequencies of the *BDNF* (rs6265) variation and cholesterol. This indicates that individuals with different genotypes had significantly different cholesterol levels. However, insignificant associations were observed between the *BDNF* (rs6265) variation and neck circumference, triglycerides, HDL, LDL, and VLDL, in line with the study conducted by Rana et al., 2018 (Rana et al., 2018). These findings are somewhat inconsistent with a previous study conducted by Abaj et al., 2021 (Abaj et al., 2021). The lack of significant associations in this study may be attributed to various factors such as sample size, population characteristics, or other genetic and environmental influences.

Molecular docking was performed by using the online docking tool called the ClusPro to evaluate the effect of mutation on the binding affinity of BDNF and TrkB. The docking score is a numerical value that indicates the quality of the predicted binding between two molecules, such as a ligand (BDNF) and a receptor (TrkB protein). In molecular docking, the score is typically calculated based on various factors, including the complementarity of shapes and electrostatic interactions between the molecules, as well as the stability of the resulting complex. The docking scores are often negative because they represent the change in free energy upon binding. In other words, a more negative docking score indicates a stronger interaction and a more favorable binding between the molecules. This convention allows for easy interpretation: the more negative the score, the more energetically favorable the binding interaction is.

The analysis using the ClusPro docking server revealed a docking score of -1217.5 kcal/mol for the wild type BDNF and TrkB protein complex. Further analysis of the interaction interface through the PDBsum online server highlighted the presence of three salt bridges, eight hydrogen bonds, and 166 non-bonded contacts in the complex. PDBsum is an online server that provides a comprehensive analysis of protein structures deposited in the Protein Data Bank (PDB). It offers a range of tools and resources to facilitate the exploration and interpretation of protein structure data. PDBsum generates concise summaries of protein structures, including information about the overall structure, secondary structure elements, ligands, and binding sites. These summaries provide a quick overview of the key features of a protein structure and aid in its interpretation. The server offers interactive 3D visualization tools that allow users to explore protein structures in detail. These tools enable the manipulation and rotation of structures, highlighting specific residues or regions of interest. Users can also generate high-quality images and download structure files for further analysis. The resulting complexes were virtualized, and the interacting amino acid residues were labeled by using PyMOL software (DeLano & Bromberg, 2004).

Specifically, hydrogen bonds were observed between the amino acid residues Glu146-Ala29, Lys196-Asp474, Gln159-Asn521, Arg199-His586, Arg168-Ala11, Met95-His8, and Ser165-Arg14. Additionally, salt bridges were formed between Lys196-Asp474, Arg199-Glu590, and Arg154-Asp475 amino acid residues. The analysis of the interaction between a mutant BDNF and TrkB protein complex was conducted to assess the impact of a mutation on the binding efficiency. The docking score for the mutant BDNF-TrkB complex generated by the cluspro online server was -1211 kcal/mol. The analysis of the interaction interface by the PDBsum online server revealed that the complex between mutant BDNF and TrkB protein forms only seven hydrogen bonds and 167 non-bonded contacts. The hydrogen bonds formed between Asn127-Ser165, Asn23-Ser188, Glu130-Tyr90, Glu82-Thr91, His124-Leu96, Trp90-Ser97, and Trp90-Gln99 amino acid residues.

The docking score for the mutant BDNF-TrkB complex, is lower (-1211 kcal/mol, i.e., less negative) than the docking score for the wild-type complex (-1217.5 kcal/mol), in line with the study conducted by Massa et al., this suggests that BDNF mutation can reduce binding affinity between BDNF and TrKB (Massa et al., 2010). In molecular docking, a more negative docking score indicates a stronger binding affinity. Therefore, the lower docking score for the mutant complex

suggests a weaker binding affinity between the mutant BDNF and TrkB protein. The analysis of the interaction interface revealed that the mutant BDNF-TrkB complex forms only seven hydrogen bonds and 167 non-bonded contacts. In contrast, the wild-type complex formed three salt bridges and eight hydrogen bonds. Salt bridges and hydrogen bonds are key interactions contributing to the stability of protein complexes. The reduced number of salt bridges and hydrogen bonds in the mutant complex indicates a weaker interaction between the mutant BDNF and TrkB protein compared to the wild-type complex. Overall, the combination of a lower docking score and fewer hydrogen bonds in the mutant BDNF-TrkB complex suggests a reduced binding affinity compared to the wild-type complex. This reduction in binding affinity has the potential to disrupt the BDNF-TrkB signaling pathway, which may consequently impact energy homeostasis (Brandon Podyma et al., 2021). However, it is important to note that this is still an area of ongoing research, and further study is necessary to fully understand the mechanisms involved.

CONCLUSION

This study examined the genetic association of the BDNF (rs6265) polymorphism with anthropometric indices and lipid profiles in Pakistani subjects. Obese subjects showed increased hip circumference, body fat percentage, and BMI. Lipid profile analysis indicated elevated triglycerides and VLDL and lower HDL levels in obese subjects. The genotyping analysis identified a significant association between the BDNF (rs6265) variation and obesity, as well as with anthropometric measurements and lipid profile parameters. The findings also revealed that the rs6265 polymorphism reduces the binding affinity between BDNF and its receptor TrkB. BDNF may serve as a genetic market for obesity. However, broader research with larger, more diverse samples is recommended to better understand the genetic and environmental factors contributing to obesity.

AUTHOR CONTRIBUTIONS

Faheem Mustafa performed research, analysed data and wrote paper. Wajiha Kanwal, Rabiatul Adawiyah Umar, and Mouvez Zeeshan performed research. Wan Rohani Wan Taib and Atif Amin Baig designed and supervised the research.

ETHICS APPROVAL

Ethical approval was obtained from the UniSZA Human Research Ethics Committee (UHREC) on August 04, 2022, with the reference number: UniSZA/UHREC/2022/388 and from the Office of Research Innovation and Commercialization (ORIC), University of Management and Technology, Lahore, Pakistan on August 08, 2021, with reference number: RE-009-2021. Consent was taken from participants prior to data collection.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in this work.

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