Investigation of Transmembrane Protein 18 (TMEM18) and Neuronal Growth Regulator 1 (NEGR1) Gene Polymorphisms' Effects on Body Mass Index in Obese Patients

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OVERVIEW

Obesity is a complex disorder which has reached epidemic proportions in many parts of the world. Genome wide association studies (GWAS) have identified more than 50 genetic loci associated with body mass and obesity in the last decade.

In this study, NEGR1 gene rs2815752 and TMEM18 gene rs6548238 single nucleotide polymorphisms (SNPs) were investigated for association in a sample of obesity patients who reside in Afyonkarahisar province.

This was a case-control study. Polymorphisms were genotyped for 172 obese patients and 77 healthy controls in LightCycler® 480.

According to obtained results, there were no significant differences between obese and controls in terms of allele and genotype frequencies of NEGR1 gene rs2815752 and TMEM18 gene rs6548238 polymorphisms. Also there were no significant differences between obese patients with regard to anthropometric and body composition parameters for rs2815752 polymorphism. However, several significant differences were found for rs6548238 polymorphism with regard to anthropometric measurements and body composition.

Consequently, there are no significant differences in NEGR1 gene rs2815752 and TMEM18 gene rs6548238 polymorphisms for genotype and allele frequencies comparing the obese group and controls. Similarly, no significant association was found for anthropometric measurements and body composition parameters within obese patients for rs2815752 while there were significant differences for rs6548238 polymorphism.

Keywords: Obesity; Polymorphism; BMI; NEGR1; TMEM18

INTRODUCTION

Obesity is a complex result of genetic background and environmental interaction (Ashrafi, 2007). Despite all efforts to prevent it, it has increased worldwide in the last 20 years (Moreno et al., 2011). However, the presence of healthy humans in the obesogenic environment has led to the search for genetic susceptibility variants that direct phenotypic expression (Hoed and Loos, 2014). It was reported that genetic heritability changes between 40% and 70% for BMI and/or obesity by twin and family studies (Melissa and Vaisse, 2009). Common characteritics of GWAS gene variants are to control feeding behavior via hypothalamus region or influence obesity related cells i.e. adipocyte cells (Fall and Ingelsson, 2014; Willer et al., 2009; Speliotes et al., 2010). The two prominent genome-wide association study (GWAS) gene variants are Transmembrane Protein (TMEM18) and Neuronal Growth Regulator 1 (NEGR1) (Loos, 2012).

NEGR1 gene discovered as a neurone specific cell adhesion molecule that belongs to the immunoglobulin (Ig) superfamily and regulates mice body weight by hypothalamus (McCormack, 2014) (Lee et al., 2012).

TMEM18 was discovered as a novel modulator that regulates neural stem cell migration towards glioma in the rat brain (Jurvansuu et al., 2008). Unlike the classical homeostatic energy models, TMEM18 expression shows its effect by altered expression levels in body cells but not in brain cells (Almén et al., 2010).

In this study, it was aimed to investigate the relationship between NEGR1 rs2815752 and TMEM18 rs6548238 polymorphisms and obesity in 172 obese and 77 controls.

MATERIAL&METHODS

Samples
BMI ranges were 18,5 - 24,9 kg/m^2 for 77 healthy controls and over 30 kg/m^2 for 172 obese individuals.

Body Composition Analysis
Bioelectrical impedance analysis was performed with TANITA BF 350 device.

Genotyping
LightCycler® 480 system was used for genotype analysis.

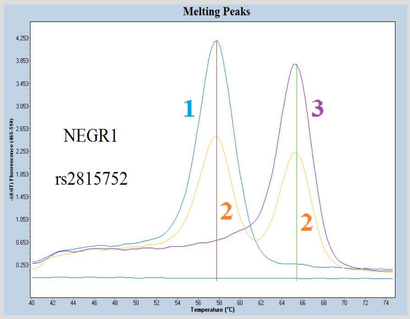


Figure 1: NEGR1 gene rs2815752 polymorphism melting curve graph (**1:**AA genotype, **2:** AG genotype, **3:** GG genotype)

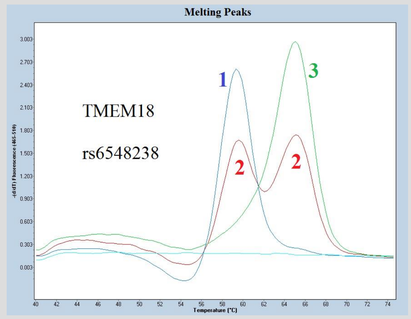


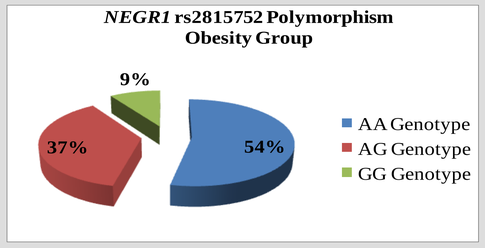
Figure 2: TMEM18 gene rs6548238 polymorphism melting curve graph (**1:**TT genotype, **2:** TC genotype, **3:** CC genotype).

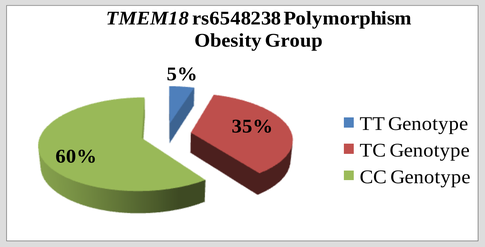
Statistics .
Statistical analyzes were performed using SPSS version 20.

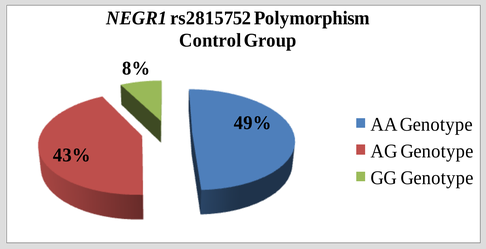
Acknowledgements

This research was supported by the Afyon Kocatepe University Scientific Research Projects Commission with a project numbered as 15SAG.11.

RESULTS







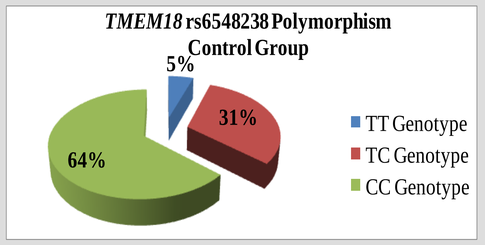


Figure 3: Genotypic distributions of NEGR1 rs2815752 and TMEM18 rs6548238 polymorphisms in obese and control groups.

Table 1: Association of NEGR1 rs2815752 and TMEM18 rs6548238 polymorphism genotypes for anthropometric measurement and body composition parameters in obese patient group.

	Rs2815752 polymorphism			**Rs6548238 polymorphism**	
	Ortalama	***p***		**Ortalama**	***p***
Height (cm)	159.6 ± 6.4	0.465		162.9 ± 9.2	**0.020***
	161.9 ± 9.3			160.3 ± 8.9	
BMI (kg/m^2)	38.2 ± 7.4	0.454		36.8 ± 6.0	0.059
	36.5 ± 5.6			36.6 ± 5.6	
Body water (kg)	40.1 ± 5.8	0.451		42.2 ± 7.8	**0.017***
	41.6 ± 7.4			40.7 ± 6.6	
Body water percentage (%)	41.9 ± 5.3	0.166		43.5 ± 5.8	**0.024***
	43.7 ± 5.6			43.7 ± 5.4	
Body fat percentage (%)	42.8 ± 8.5	0.237		40.3 ± 8.7	**0.006***
	40.0 ± 8.6			40.3 ± 8.5	
Lean body mass (kg)	54.6 ± 7.8	0.524		57.7 ± 11.6	**0.021***
	57.0 ± 11.2			55.7 ± 9.9	

CONCLUSION

As a conclusion, we could not demonstrate any association for NEGR1 or TMEM18 gene polymorphisms and obesity risk between our study groups through genotype distribution and allele frequency. However TMEM18 gene polymorphism was associated with anthropometric measurements and body composition parameters through risk allele oriented grouping within obese patients. More effective and population oriented genetic identifications would be possible when the components of "missing heritage" were determinated. In this context, our study aimed to contribute literature data by investigation of 2 important SNP in the Turkish population for the first time. Nevertheless, following points needs to be reconsidered to unravel obesity genetic (i) to study with obesity subgroups (ii) to analyze other SNP variations in the same gene regions (iii) to investigate functional effects of SNP variations (iv) to create classification parameters that include gene-environment interaction (v) to replicate researchs in larger population samples.

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