Are Common Melanocortin-3 Receptor Polymorphisms Associated with an Increased Risk of Obesity in Childhood?

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BACKGROUND

Obesity is currently a global health concern, with over 1.9 billion adults being overweight worldwide [1]. The prevalence of obesity is projected to increase by 33% over the next two decades [2]. Obesity is a major risk factor for chronic conditions such as diabetes and cardiovascular disease [3, 4]; obese children also experience respiratory problems, hypertension, and negative psychological effects [5].

Obesity is a multifactorial condition, with both environmental and genetic factors playing a role in its development [6]. Specifically, one gene of interest, the melanocortin-3 receptor (MC3R) gene, is a 7-transmembrane G-protein coupled receptor that regulates several biological functions [7], including energy homeostasis, energy storage, and the ability to convert food into adipose tissue [8]. Two polymorphisms in this gene, Thr6Lys (T6K) and Val81Ile (V81I), are significantly correlated with increased adiposity in childhood, greater body and fat mass, and higher insulin and leptin levels [9].

OBJECTIVE

This meta-analysis aimed to examine and synthesize evidence on the association between the MC3R polymorphisms, T6K and V81I, and their effect on the development of obesity in children.

METHODOLOGY

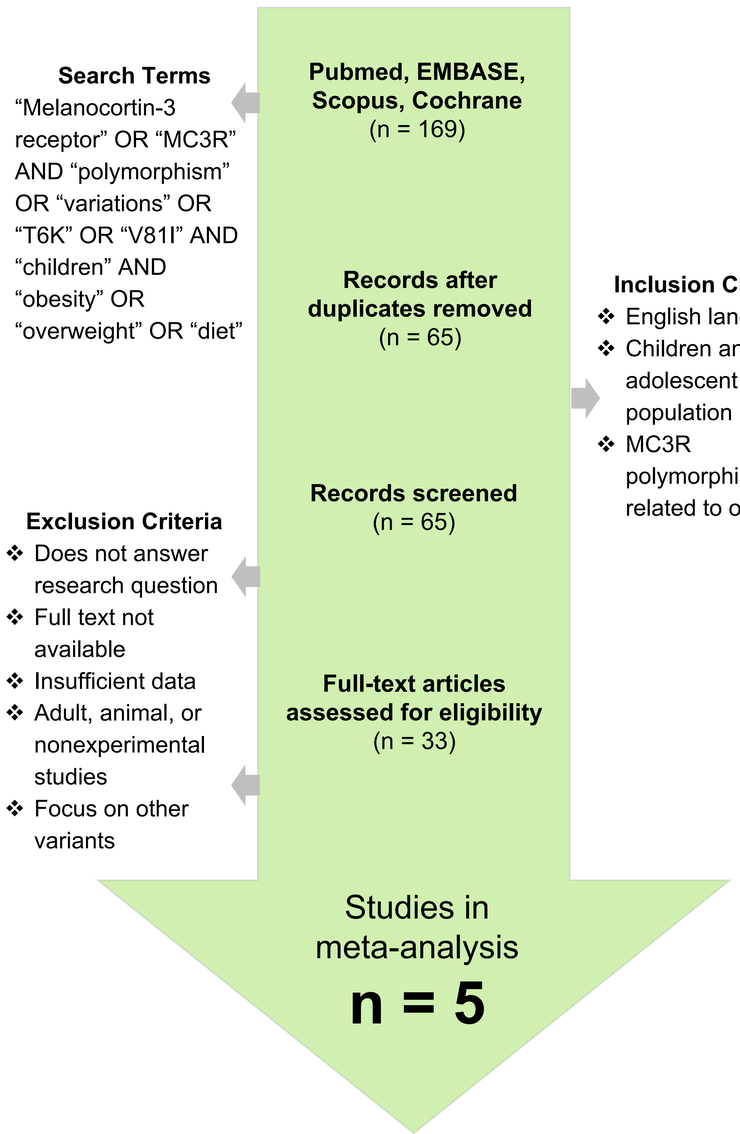


Figure 1. Flow chart illustrating the literature search and inclusion / exclusion process

RESULTS

Table 1. Characteristics of the included studies for the association between childhood obesity and T6K and V81I

Study	Population	Methodology & Design	Findings
Aris et al. (2016)[6]	• 1090 Chinese, Malay, and Indian infants • Birth to 48 months • Singaporean population	**Prospective cohort study, interim case-control analysis** • Infant anthropometry measurements were collected until age 2 • Genotyping of MC3R variants was performed • Obesity was classified as having BMI ≥ 95th percentile for age and sex • Mothers used questionnaires to record infant feeding	• There was an association between MC3R and early childhood adiposity in first 48 months, and slowness-in-eating at 12 months • Each additional copy of an MC3R allele resulted in an increased odds of overweight by 1.48 times (95% CI: 1.17-1.88) and obesity by 1.58 (95% CI: 1.10-2.28)
Cieslak et al. (2013)[10]	• 257 obese children, ages 4-17 • 94 non-obese controls • Polish population	**Case-control study** • Genotypes were screened for MC3R polymorphisms • Obesity was defined as having relative BMI values greater than 120% of standard BMI • Kruskal-Wallis test was used to determine the association	• V81I is neutral and does not affect receptor ligand binding ability • Ile335Ser is associated with an increased risk of obesity
Feng et al. (2005)[11]	• 190 overweight and 165 non-overweight African-American and Caucasian children • Ages 5-18 • US population	**Case-control study** • Anthropometry measurements of subjects were obtained • Genotyping for MC3R polymorphisms was performed • Obesity was classified as having BMI ≥ 95th percentile for age and sex	• Homozygosity for both T6K and V81I was associated with impaired cAMP generation and greater BMI, leptin and insulin levels • Double homozygosity bound approximately 60% less α-MSH
Savastano et al. (2009)[9]	• 416 healthy and overweight children and adolescents • Ages 6-19 • US population	**Experimental study, joint data analysis** • Healthy children in 3 non-intervention metabolic protocols and overweight children in 2 weight-loss treatment studies were recruited • Obesity was classified as having BMI ≥ 95th percentile for age and sex • Energy intake of subjects was studied through a 9835-kcal food array, resting energy expenditure, or total daily energy expenditure	• Homozygosity was correlated with greater body and fat intake • 2138InsCAGACC was not significantly associated with obesity
Yako et al. (2011)[12]	• 227 obese-overweight and 204 normal weight black and colored children • Ages 11-16 • South African population	**Case-control study** • Body composition was measured and genotyping was performed • Statistical analyses were stratified by ethnicity • BMI greater than 25 kg/m^2 and 30 kg/m^2 was classified as overweight and obese respectively	• T6K and V81I were both associated with obesity and cholesterol only in colored pupils • T6K was also linked to blood pressure and triglyceride levels

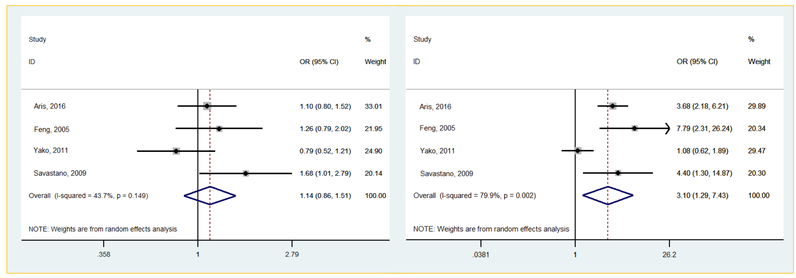


Figure 2. Forest plot of T6K studies describing the association between obesity and heterozygous (left) and homozygous (right) genotypes. OR indicates odds ratio; CI, confidence interval.

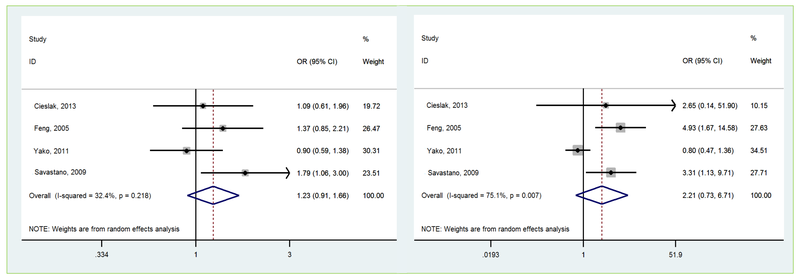


Figure 3. Forest plot of V81I studies describing the association between obesity and heterozygous (left) and homozygous (right) genotypes. OR indicates odds ratio; CI, confidence interval.

DISCUSSION

The results indicated that homozygous genotypes for T6K were associated with a 3.10-fold increased risk of overweight / obesity in children. However, this association was not significant in this pooled sample of children with homozygous V81I alleles. The heterozygotes of either T6K or V81I were not associated with overweight / obesity. Taken together, our results supported a recessive inheritance model for MC3R gene with respect to obesity.

The mechanism in which MC3R increases adiposity is related to its role in regulating energy homeostasis, specifically by increasing food intake and feeding efficiency [13]. In MC3R-deficient mice, calories are more readily stored as fat because of higher efficiency [14]. In humans, homozygous children were reported to have difficulty with weight loss due to an inability to increase feeding efficiency [15]. Additionally, heterozygous and homozygous individuals with T6K and V81I were reported to have elevated free fatty acids, low rates of lipid oxidation [9, 16], and decreased insulin to glucose ratio and fasting glucose due to high rates of glucose oxidation [16].

Limitations

Varying definitions of obesity: definitions were not consistent across studies, making them difficult to compare and resulting in high heterogeneity

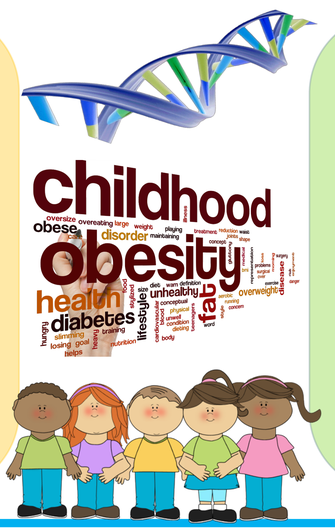
Small number of studies: potential overestimation of association

Low external validity: results are not generalizable due to small sample sizes and since the studies were targeted towards specific populations

Significant heterogeneity: indicates presence of unidentified sources of uncertainties

Availability of data: many studies were excluded, as important data was unavailable

Foreign language exclusion bias, **ease of access**



Future Considerations

- **Standardize** the definition for overweight and obesity
- Conduct studies specifically on weight trajectory in **child and adolescent** populations
- More focus on the effects of **other MC3R polymorphisms** on obesity
- Study effects of interaction between other **melanocortin-receptor genes**
- Investigate effects of MC3R variants with regards to **eating patterns** and obesity

CONCLUSION

The results of this meta-analysis, n = 5, confirmed a significant association between the homozygous T6K genotype and an increased risk of childhood obesity.

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