Are Common Melanocortin-3 Receptor Polymorphisms Associated with an Increased Risk of Obesity in Childhood?
Charita Koya, Meng-Che Tsai, Carol Strong, Tsung Yu
Faculty of Health Sciences, University of Ottawa

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, Thr3Lys (T6K) and Val811le (V811I), are significantly correlated with increased adiposity in childhood, greater body 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 V811I, and their effect on the development of obesity in children.

METHODOLOGY

Search Terms
“Melanocortin-3 receptor” OR “MC3R” AND “polymorphism” OR “variations” OR “T6K” OR “V811I” AND “obesity” AND “obese” OR “overweight” OR “diet”

Pubmed, EMBASE, Scopus, Cochrane (n = 169)

Records after duplicates removed (n = 65)

Inclusion Criteria
- English language
- Children and adolescent population
- MC3R polymorphisms related to obesity

Records screened (n = 65)

Exclusion Criteria
- Does not answer research question
- Full text not available
- Insufficient data
- Adult, animal, or nonexperimental studies
- Focus on other variants

Full-text articles assessed for eligibility (n = 33)

Studies in meta-analysis
n = 5

RESULTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Prospective cohort study, interim case-control analysis</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arns et al. (2016)</td>
<td>1060 Chinese, Malay, and Indian infants</td>
<td>Infant anthropometry measurements were collected until age 2</td>
<td>There was an association between MC3R and early childhood adiposity in first 48 months, and slowness in gaining at 12 months. Each additional copy of an MC3R allele resulted in an increased odds of overweight by 1.48 (95% CI 1.07-2.02) and obesity by 1.34 (95% CI 1.05-2.70).</td>
</tr>
<tr>
<td>Cislaghi et al. (2012)</td>
<td>277 obese children, ages 4-17</td>
<td>Genotypes were screened for MC3R polymorphisms</td>
<td>Case-control study: MC3R homozygous Ile335Ser was associated with obesity and 60% less fat loss.</td>
</tr>
<tr>
<td>Feng et al. (2009)</td>
<td>150 overweight and 155 non-overweight African-American and Caucasian children</td>
<td>Anthropometry measurements of subjects were obtained</td>
<td>Case-control study: Genotyping for MC3R polymorphisms was performed. Overall, obesity was classified as having BMI &gt; 95th percentile for age and sex.</td>
</tr>
<tr>
<td>Savova et al. (2009)</td>
<td>416 healthy and overweight children and adolescents</td>
<td>Healthy children in 3 non-intervention metabolic protocols and overweight children in 2 weight-loss treatment studies were recruited</td>
<td>Experimental study, joint data analysis: MC3R homozygous Ile335Ser was associated with high BMI.</td>
</tr>
<tr>
<td>Yoku et al. (2011)</td>
<td>227 obese-overweight and 204 normal weight black and colored children</td>
<td>Body composition was measured and genotyping was performed</td>
<td>Case-control study: BMI greater than 25 kg/m2 and 30 kg/m2 was classified as overweight and obese respectively.</td>
</tr>
</tbody>
</table>

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 V811I 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 V811I alleles. The heterozygotes of either T6K or V811I 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 V811I 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].

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.

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

REFERENCES

ACKNOWLEDGEMENTS
I would like to thank Dr. Meng-Che Tsai and Dr. Carol Strong for their continual support and guidance throughout this project, as well do Dr. Tsung Yu for further assistance. I would also like to thank the University of Ottawa for providing me with this valuable experience.

Contact Information
Charita Koya
Email: ckoaya012@uottawa.ca