Serotonin system genes contribute to the susceptibility to obesity in Black adolescents

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Abstract

Objective: The importance of the central and peripheral serotonin systems in regulating energy balance and obesity development has been highlighted in animal models. Yet, the role of both serotonin systems has not been systematically assessed in humans. The purpose of this study was to investigate the association of genes within both serotonin systems with obesity outcomes in black adolescents.

Methods: African–American adolescents (n = 1052) whose mothers participated the Memphis New Mother’s Study were assessed. In total, 110 polymorphisms mapped to 10 serotonin genes were examined for their associations with standardized body mass index (BMI-z) scores and waist circumferences using generalized estimating equation models.

Results: Over 39% of adolescents were overweight or had obesity. Three single nucleotide polymorphisms (SNPs) within TPH2, HTR3B, and SLC6A4, were significantly associated with BMI-z scores (p < 1.7 × 10⁻³). Two SNPs in TPH2 were nominally associated with waist circumferences. One SNP in HTR2C was associated with BMI-z scores (p = 0.001) and waist circumferences (p = 0.005) only in girls. Tissue-specific expression indicates that three identified genes are predominantly expressed in the brain.

Conclusion: The central serotonin system may play a key role in obesity development in black adolescents. Future studies are warranted to explore additional serotonin system genes and their potential obesogenic mechanisms in humans.

Keywords

adolescents, African–American, childhood obesity, serotonin

1 INTRODUCTION

Recent studies in rodents have shed light on the important role of the serotonin (5-hydroxytryptamine [5-HT]) pathways in the development of obesity.1-3 5-HT in the central nervous system has been identified as participating in the regulation of appetite, food intake, and glucose homeostasis in the hypothalamus and the brain stem nucleus of the solitary tract.4,5 It also modulates the thermogenic function in brown adipose tissue through the sympathetic system.2 In addition to a role in the central 5-HT system, 5-HT derived from the peripheral tissues has recently been discovered to modulate lipid metabolism, hepatic glucose production, and energy expenditure.1,3 In particular, potential obesogenic mechanisms involved in the peripheral 5-HT system include regulation of the browning process,
thermogenesis, and lipolysis in adipose tissues and energy expenditure in skeletal muscles. The broad effects of the central and peripheral 5-HT systems on energy homeostasis have driven a growing interest in their potential as weight loss therapeutic targets.

5-HT is synthesized from l-tryptophan through the activity of tryptophan hydroxylases (TPHs). TPH1 is predominantly expressed in peripheral tissues, such as intestinal enterochromaffin cells, pancreatic and liver cells, and adipose tissue, whilst TPH2 is primarily expressed in the brain. The function of 5-HT is mediated through binding to different serotonin receptors (HTRs, seven subfamilies), expressed on neurons or in peripheral tissues. The availability of 5-HT further regulated by its reuptake through the transporter encoded by the SLC6A4 gene and catabolized by monoamine oxidase. Since the 5-HT systems play an important role in energy regulation in rodent models, this role may also be conserved in humans. Examination of variations within the 5-HT system genes may identify a contribution to the development of obesity in humans. To date, the most frequently assessed genetic variations within the 5-HT systems related to obesity are located at the SLC6A4 gene, although findings are not consistent. Variations in SLC6A4 have also been linked with obesogenic eating behaviors, such as appetite, energy intake, dis-inhibited eating, and emotional eating. In addition to SLC6A4, several 5-HT receptor genes and TPHs, including HTR1B, HTR2A, HTR2B, HTR2C, HTR6, HTR7, TPH1, and TPH2 have also been assessed for potential associations with body weight measures and/or eating behaviors. However, the majority of the results have been inconsistent.

Although multiple genes within the 5-HT systems have been examined for their associations with obesity, individual studies have typically focused on one or two genes within the systems and have not systematically evaluated if both the central and peripheral 5-HT systems play a role in obesity development in humans. Therefore, the purpose of this study was to investigate the association of genetic variants mapped to ten genes within the central and peripheral 5-HT systems with obesity outcomes in African-American adolescents, a group with a high prevalence of obesity. Genes within both central and peripheral 5-HT systems were hypothesized to be associated with obesity outcomes.

2 | METHODS

2.1 | Study design and population

African-American adolescents (n = 1168) whose mothers participated the Memphis New Mother’s Study (NMS) were included in this study initially. In brief, NMS was a randomized controlled trial that investigated the effect of the nurse–family partnership home visiting program on pregnancy outcomes and maternal and child health. The original cohort of women and their offspring were assessed at an 18-year follow-up assessment between 2008 and 2013. During the assessment, saliva samples and sociodemographic data were collected from two groups of offspring: 600 index children who were born during the initial NMS study and 568 subsequent children who were born within 5 years of the index children. The NMS study and the current study were both approved by the university Institutional Review Board.

2.2 | Anthropometric, sociodemographic, and lifestyle measures

Height, weight, and waist circumference were measured in each offspring. Age- and sex-specific body mass index (BMI) percentiles and standardized BMI (BMI-z) scores were calculated according to the Centers for Disease Control growth curve data (https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm). Because the current study focused on adolescents, offspring participants whose ages were more than 20 years old were excluded (n = 41). Smoking was reported as smoking during the past 6 months (yes or no). Alcohol intake was categorized based on the times of drinking during the past month (0, 1–2, >2). Illicit drug use was reported as usage of illicit drug during the past month (yes or no). Education was divided according to whether participants graduated from high school or passed high school equivalency (yes or no). Parity was grouped based on the number of live births delivered by the female participants (0, 1, >1); male participants were coded as “0.” Participants (n = 14) with missing data on anthropometric and sociodemographic measures were also excluded.

2.3 | Genotyping of genes with the serotonin pathways and ancestry informative markers

Saliva samples were collected using Oragene collection and preservation kits (DNA Genotek). DNA was extracted following the manufacture’s standard protocol. A total of 109 single nucleotide polymorphisms (SNPs) and the 5-HTTLPR polymorphism mapping to ten 5-HT pathway genes, including TPH1, TPH2, SLC6A4, HTR1A, HTR1B, HTR2A, HTR2B, HTR2C, HTR3A, and HTR3B were assessed using the Illumina GoldenGate assay (see Table S1). SNPs were excluded from the analyses, if (1) genotype call rate <0.8, (2) minor allele frequency <1%, (3) Hardy–Weinberg equilibrium test of p < 1 × 10⁻⁶. Additionally, five participants were excluded from the subsequent children group because they were identical twins and had relatively lower genotyping rates.

To avoid spurious genetic associations resulting from the population structure, 186 ancestry informative markers (AIMs) were genotyped and AIMs scores were generated to represent participants’ ancestry make-up and population structure. To reduce heterogeneity, participants with minimum African ancestry scores were excluded (scores < 0.05; n = 39 index children; n = 17 subsequent children). The remaining adolescents had African ancestry scores between 0.394 and 0.968. The AIMs scores were also used as covariates in the subsequent genetic analyses to control population structure.
2.4 | Statistical analysis

Obesity outcomes included BMI-z score and waist circumference. Waist circumference was transformed \((1/\text{square of waist})\) to fit a normal distribution. BMI percentile was not included as an obesity outcome because its transformations did not fit a normal distribution (Kolmogorov–Smirnov test \(p < 0.001\)). Covariates, including age, gender, education, parity, smoking, alcohol intake, illicit drug use, maternal treatment status during the initial NMS study, and AIMS, were adjusted in the analyses due to their potential effects on obesity measures. Adolescents from the initial maternal treatment and control groups were combined for the genetic analyses because maternal treatment status was not significantly associated with adolescents’ obesity measures \((p = 0.63)\).

Descriptive statistics were used to summarize the characteristics of the participants. Generalized estimating equation (GEE) models were used to control family cluster and examine the association of SNPs with obesity outcomes. Three genetic models (i.e., additive, dominant, and recessive) were assessed separately. Bonferroni-adjusted significance level \((p < 1.7 \times 10^{-3})\) was used to correct for multiple testing with ten genes and three genetic models. Additionally, identified SNPs were assessed in the two adolescent groups, respectively. SNPs mapped to the HTR2C gene were analyzed in males and females, separately, because it locates on the X chromosome and its inheritance pattern and genetic effect may be different between males and females. All analyses were conducted using STATA 15.0.

To assess the combined effect of the 5-HT pathway on obesity outcomes, genetic risk score (GRS) was created using the identified SNPs (calculation of the GRS is described in Table S1). GEE was used to estimate the association of GRS with BMI and waist circumference adjusting for covariates.

2.5 | Functional inference

Functional relevance of the identified SNPs was annotated using HaploReg v4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php). Tissue-specific expression pattern was assessed using GTEx portal (https://gtexportal.org). Ontological analysis of each annotated gene was conducted using ToppFun (https://toppgene.cchmc.org/enrichment.jsp).

3 | RESULTS

3.1 | Participants characteristics

There were 1052 African–American adolescents who were included in the final analysis. Their ages ranged from 14 to 19 years old (Table 1). Over 39% of adolescents \((n = 413)\) were within the category of overweight or obesity. The prevalence of overweight and obesity was more common in girls than in boys (48.3% vs. 29.6%; \(p < 0.001\)). Average waist circumference was 31.8 inches with a range between 22 and 59 inches. Among all of the adjusted demographic and behavior risk factors, only sex was significantly related to BMI-z scores \((p = 0.0001)\).

3.2 | Association of serotonin pathway genes with obesity outcomes

Three SNPs, rs11179071 close to TPH2, rs2276307 in HTR3B, and rs9903062 in SLC6A4, were significantly associated with BMI-z scores \((p < 1.7 \times 10^{-3})\) (Table 2). One SNP, rs7055144 in HTR2C, was only associated with BMI-z scores \((p = 0.001)\) in adolescent girls. Each copy of the minor allele \((A)\) of rs11179071 increased BMI-z score by 0.24 (95% confidence interval [CI]: 0.12–0.35). Each copy of the minor allele \((G)\) of rs2276307 decreased BMI-z score by 0.26 (95% CI: \(-0.41\) to \(-0.1\)). The AA genotype of rs9903062 was associated with higher BMI-z scores than the AG and GG genotypes \((b = 0.63, 95\% \text{ CI}: 0.54–0.72)\). When adolescents with overweight/obesity were compared to those with normal weight, each copy of the minor allele \((A)\) of rs11179071 increased the odds of overweight and obesity (additive genetic model, odds ratio = 1.31/allele, 95% CI: 1.02–1.68). Each copy of the minor allele \((G)\) of rs2276307 decreased the odds of overweight/obesity (additive genetic model, odds ratio = 0.58/allele, 95% CI: 0.42–0.81). The odds ratio of the AA genotype of rs9903062 was not estimated due to limited number of adolescents with overweight/obesity carrying AA alleles. In adolescent girls, the carriers with CC alleles of rs7055144 had higher BMI-z scores (recessive genetic model, \(b = 0.16, 95\% \text{ CI}: 0.06–0.25\) and higher odds of overweight/obesity than those with CT and TT genotypes (odds ratio = 1.37, 95% CI: 1.1–1.71). When these SNPs were assessed in the index and subsequent children separately, they were also nominally significantly associated with BMI-z scores with consistent coefficient direction both in the index and subsequent children groups, except for rs7055144 in the subsequent children group \((p = 0.08)\).

None of the SNPs were significantly associated with waist circumferences after adjusting for multiple testing. Two SNPs, rs11179071 and rs10506647 in TPH2, were nominally significantly associated with waist circumferences with consistent coefficient direction in the entire adolescents, the index, and the subsequent children groups, respectively \((p < 0.05, \text{ Table 2})\). Also, rs7055144 in HTR2C was nominally associated with waist circumferences in adolescent girls \((p = 0.005)\). The minor allele \((A)\) of rs11179071 and CC alleles of rs7055144 were associated with increased waist circumferences, consistent with their associations with BMI-z scores (waist circumferences were inversely transformed). The carriers of the TT genotype of rs10506647 had higher waist circumferences than those with the TC and CC genotypes.

Unweighted GRS was created using the identified SNPs, rs11179071, rs2276307, rs9903062, and rs10506647, to assess the accumulative effect of the serotonin pathway on obesity outcomes.
The SNP, rs7055144, was not included in the GRS calculation due to its distinct impact on girls and not on boys. The range of the GRSs was from 0 to 4. The GRSs were significantly associated with BMI-z scores \( p < 0.0001 \); Figure 1A. A higher score was associated with a greater BMI-z score \( (b = 0.26, 95\% \text{ CI: } 0.17–0.36) \) and increased risk of overweight/obesity \( (\text{odds ratio } = 1.49, 95\% \text{ CI: } 1.21–1.83) \). The GRSs were also positively significantly associated with waist circumferences \( p < 0.0001 \); Figure 1B.

### 3.3 Ontological analysis of the identified SNPs and genes

Functional relevance of the five identified SNPs and SNPs in linkage disequilibrium \( \left( \text{LD; } R^2 \geq 0.8 \right) \) was analyzed using HaploReg. Three SNPs, rs2276307, rs9903062, and rs10506647, and SNPs in LD reside within promoter histone markers, enhancer histone markers, or DNAse hypersensitive regions. Tissue-specific expression levels were analyzed using GTEx portal for the four identified 5-HT pathway genes, TPH2, HTR3B, SLC6A4, and HTR2C. Three of these genes, except for SLC6A4, are predominantly expressed in the brain. Ontological analyses were also conducted for these 5-HT pathway genes using ToppFun. These genes were associated with obesity related human diseases and mouse phenotypes, such as appetite, body temperature, activity, and stress (Figure 2).

### 4 DISCUSSION

The purpose of this study was to assess the relationship between the serotonin pathway and obesity outcomes in African-American adolescents. The results indicated that four 5-HT pathway genes, TPH2 \( (\text{rs11179071, rs10506647}) \), HTR3B \( (\text{rs2276307}) \), SLC6A4 \( (\text{rs9903062}) \), and HTR2C \( (\text{rs7055144}) \) were associated with BMI-z scores. The GRSs that combined the effects of the identified SNPs was also significantly associated with BMI-z scores and waist circumferences. Specifically, adolescents with higher GRSs had increased odds of overweight and obesity and larger waist circumferences. Functional analysis indicated three identified SNPs are located within cis-regulatory elements and possibly participate in transcription regulation of relevant genes. In addition, the majority of the identified genes are prominently expressed in the brain, which implies the potential role of the central 5-HT system in the development of obesity in African-American adolescents. The obesogenic mechanisms that these 5-HT pathway genes are likely to be involved in eating regulation,
TABLE 2 Significant associations of serotonin pathway genes with obesity outcomes

| SNP    | Chr | Position | Genetic model | Gene   | MA | MAF   | Total b  | p     | 95% CI          | Index b | p     | Subsequent b | p     |
|--------|-----|----------|---------------|--------|----|-------|----------|-------|-----------------|---------|-------|---------------|-------|
|        |     |          |               |        |    |       |          |       |                 |         |       |               |       |
| Outcome: BMI-z score |
| rs11179071 | 12 | Intergenic | Additive/dominant$^b$ | TPH2   | A  | 0.13  | 0.2374  | <0.0001 | 0.1239 0.3508 | 0.2241 | 0.0045 | 0.3197 0.0002 |
| rs2276307  | 4  | Intron   | Additive/dominant$^b$ | HTR3B  | G  | 0.12  | -0.2574 | 9.5 × 10$^{-4}$ -0.4101 -0.1047 | -0.2528 | 0.0209 | -0.2898 0.004 |
| rs9903062  | 17 | Intron   | Recessive      | SLC6A4 | A  | 0.03  | 0.6334  | <0.0001 | 0.5422 0.7247 | 0.3458 | <0.0001 | 0.9226 <0.0001 |
| rs7055144b | X  | Intron   | Recessive      | HTR2C  | C  | 0.42  | 0.1585  | 0.001   | 0.0639 0.2531 | 0.2001 | 0.0012 | 0.1354 0.083  |
| Outcome: Transformed waist circumference$^c$ |
| rs11179071 | 12 | Intergenic | Additive/dominant$^*$ | TPH2   | A  | 0.13  | -5.6 × 10$^{-5}$ 0.0038 | -9.4 × 10$^{-5}$ -1.8 × 10$^{-5}$ -5.6 × 10$^{-5}$ 0.045 | -6.3 × 10$^{-5}$ 0.023 |
| rs10506647 | 12 | Intron   | Recessive      | TPH2   | T  | 0.07  | -1.2 × 10$^{-4}$ 0.0175 | -2.1 × 10$^{-4}$ -2.1 × 10$^{-5}$ -1.2 × 10$^{-4}$ 0.035 | -1.4 × 10$^{-4}$ 0.043 |
| rs7055144b | X  | Intron   | Recessive      | HTR2C  | C  | 0.42  | -4.5 × 10$^{-5}$ 0.0046 | -9.4 × 10$^{-5}$ -1.8 × 10$^{-5}$ -5 × 10$^{-5}$ 0.029 | -5.6 × 10$^{-5}$ 0.004 |

Note: GEE models adjusted for month of age, gender, maternal treatment, smoking, alcohol, drug use, parity, and education. Total represents the results obtained from the whole sample. Index represents the results obtained from the index children. Subsequent represents the results obtained from the subsequent children.

Abbreviations: b, coefficient; Chr, chromosome; CI, confidence interval; GEE, generalized estimating equation; MA, minor allele; MAF, minor allele frequency; SNP, single nucleotide polymorphism.

$^a$Both additive and dominant models were significantly associated with the obesity outcomes, but only results of additive genetic model were presented.

$^b$The results in adolescent girls.

$^c$The waist circumference was inversely transformed.
body temperature modification, sleep alteration, physical activity, and stress response.

Specifically, TPH2 participates in the biosynthesis of 5-HT in the brain. A previous study examined a SNP (rs4570625) in TPH2 in patients with Prader–Willi syndrome, a genetic disorder linked to morbid obesity, and identified the risk allele was associated with hyperphagia. In the current study, two SNPs, rs11179071 and rs10506647, mapped to TPH2 were potentially associated with obesity outcomes in African–American adolescents. Studies conducted using mouse models revealed that Tph2 knockout mice (Tph2−/−) displayed decreased food intake and reduced body weight. Conditional knockout Tph2 in caudal 5-HT neurons also affected appetite. Hence, the two identified SNPs within TPH2 may be involved in the modification of energy balance by regulating eating behaviors, such as appetite and satiety.

HTR3B encodes a subunit of 5-HT type 3 receptor and is highly expressed in several brain regions, such as the amygdala, caudate, and hippocampus. Previous studies have shown variations in HTR3B were associated with substance dependence and antiemetic therapy. The results indicated that the SNP, rs2276307, within an intron region of HTR3B might contribute to BMI variability in African–American adolescents. A potential obesogenic mechanism involving 5-HT type 3 receptor is appetite regulation. Ontological analysis indicated that HTR3B was associated with anorexia. A study in rats also found that hindbrain 5-HT could induce hypophagia by activation of 5-HT3 and 5-HT2C receptors.
Figure 2  The identified 5-HT pathway genes linked to obesity related human diseases and mouse phenotypes. The rainbow segments represent 5-HT pathway genes. The orange segments represent phenotypes in humans. The blue segments represent phenotypes in mice. The ribbons represent the associations between genes and phenotypes. 5-HT, 5-hydroxytryptamine; IGF-1, insulin-like growth factor 1; Temp, temperature.

SLC6A4 encodes 5-HT transporter which terminates the action of 5-HT by uptake into cells or presynaptic neurons. With regards to obesity, SLC6A4 is the most frequently assessed gene within the 5-HT systems. Several genetic variations mapped to this gene have been examined, which include an insertion/deletion variant within the 5-HT transporter linked polymorphic region (5-HTTLPR), and a 17-bp variable number of tandem repeats sequence in the second intron (Stin2). 5-HTTLPR was assessed in this study. Previous findings on this polymorphism were not consistent. Some studies found the S/S genotype was associated with higher BMI; some studies identified the opposite association, and the others found no association. In this study, the 5-HTTLPR polymorphism was not significantly associated with obesity outcomes. Yet, the minor allele (A) of rs9903062 within SLC6A4 was associated with increased BMI in a recessive genetic model. Previous studies found SLC6A4 was implicated in energy intake, stress induced appetite for sweets, ability to control food intake and emotional eating. In SLC6A4 knock out mice, 5-HT reuptake is absent and 5-HT concentration is markedly reduced. These mice also present decreased food intake but increased body fat and insulin resistance. Therefore, modification of eating behaviors may be potential obesogenic mechanisms in which the genetic variations within SLC6A4 are involved.

HTR2C is located on chromosome X, which encodes a G-protein coupled 5-HT receptor. This receptor is predominantly expressed in the brain, particularly nucleus accumbens, caudate, hypothalamus, and putamen according to the GTEx database. This 5-HT receptor is involved in the modulation of pro-opiomelanocortin neurons and the release of CRH and subsequently regulation of corticosterone. Therefore, HTR2C receptor plays a role in the regulation of appetite and eating behavior. It also plays a role in insulin sensitivity and glucose homeostasis. HTR2C receptor has been previously associated with weight gain induced by atypical antipsychotics. A HTR2C receptor agonist, lorcaserin (recently withdrawn from the market due to potential relationship to cancer), was approved by FDA for weight loss treatment. Previous studies have assessed the association of SNPs within HTR2C with outcomes related to obesity or weight loss. In this study, rs7055144 was associated with BMI-z scores and waist circumferences in female but not male African-American adolescents. Alternatively, Li et al. did not find a significant association of this SNP with BMI in adult European Americans. However, the association of rs7055144 was not assessed separately by sex in their study. Another SNP, rs6318, has been frequently examined in previous studies with mixed results. In the current study, rs6318 was not significantly associated with obesity outcomes, which was consistent with the findings from a recent meta-analysis on this SNP.

Several strengths and limitations need to be considered when interpreting the results from this study. A strength of the current study was that multiple SNPs within ten 5-HT system genes were assessed with a relatively homogeneous sample of African-American adolescents. Additionally, spurious genetic associations potentially arising from population structure were minimized by controlling for the AIMS. A major limitation of this study is that several 5-HT receptor genes, such as HTR1D, HTR1E, HTR6, and HTR7 were not genotyped and consequently were not assessed in this study, although common genes involved in the 5-HT systems were assessed. Future studies including more 5-HT genes are suggested to further...
validate the role of central and peripheral 5-HT systems in the development of obesity.

5 | CONCLUSION

The findings from this study suggest a potential role of the central 5-HT system in the development of obesity in African-American adolescents. Future studies are warranted to validate current results and explore potential obesogenic mechanisms associated with the 5-HT systems in humans.

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CONFLICT OF INTEREST

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Ying Meng was responsible for conceptualization, data analysis, draft preparation, and funding support; Susan W. Groth was responsible for providing the New Mother’s Study data, conceptualization, and draft editing and revision; Colin A. Hodgkinson was responsible for conceptualization, providing genetic data, and draft editing; Thomas J. Mariani was responsible for conceptualization, and draft editing. All authors have agreed to the published version of the manuscript.

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SUPPORTING INFORMATION
Additional supporting information may be found in the Supporting Information section at the end of this article.

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