Association of Dio2 Thr92ala Polymorphism With Pediatric Obesity in Japanese Children: A Case Control Study

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Research

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Abstract

Background

Genetic factors play a critical role in the onset and progression of obesity. Brown adipose tissue (BAT) activity is also critical for adiposity. The objective of this study was to evaluate the prevalence and effects of gene polymorphisms related to BAT in pediatric obesity.

Methods

A case-control study with 270 non-obese and 86 obese children was performed. All participants underwent genotyping of type 2 deiodinase (DIO2) Thr92Ala (rs225014), uncoupling protein 1 (UCP1) -3826 A/G (rs1800592), and β 3 adrenergic receptor (β 3AR) Trp64Arg (rs4994).

Results

In the case-control study, the prevalence of the homozygous Ala/Ala allele of the DIO2 gene in the obese group was 15.1 % versus 6.3 % in the non-obese group, resulting in an odds ratio (OR) of 3.393 (95% confidence intervals [CI], 1.498-7.687, $P = 0.003$). The genotype distribution of UCP1-3826 A/G and β 3AR Trp64Arg did not significantly differ between the obese and the non-obese groups, and the ORs were 1.831 (95% CI, 0.955-3.512, $P = 0.069$) and 0.819 (95% CI, 0.263-2.555, $P = 0.731$), respectively.

Conclusions

The results of this study indicate that the homozygous Ala/Ala allele of the DIO2 gene is associated with an increased risk of obesity in children.

Background

Obesity is a complex medical disease due to multiple factors, including genetic susceptibility and environmental and lifestyle factors, and is associated with an increased risk of various diseases, including cardiovascular disease, type 2 diabetes mellitus, and cancer (1). Obesity is increasing globally, even in children. Pediatric obesity tends to lead to continued obesity in adulthood; thus, the pediatric obesity epidemic is considered one of the most important health issues. Genetic factors in obesity account for 40-70 % (2) and some single-nucleotide polymorphisms (SNPs) are associated with pediatric obesity (3); thus, it is important to evaluate the genetic background in pediatric obesity.

Recently, brown adipose tissue (BAT) has been identified as a novel target of obesity, as it increases energy expenditure by non-shivering thermogenesis. BAT exists even in adulthood, but is highly present in childhood. Enhancing BAT could be an attractive strategy for combating pediatric obesity (4-6). Therefore, it is highly likely that BAT activity is critical for adiposity, and the polymorphism of genes related to BAT might cause obesity in childhood.

Type 2 deiodinase (DIO2) converts thyroxine to triiodothyronine (T3), a biologically active form. Thyroid hormone (TH) stimulates thermogenesis via the induction of mitochondrial uncoupling protein 1 (UCP1) in BAT. The thermogenic effect of BAT in response to TH is caused by the synergistic interaction with the sympathetic nervous system (SNS) through the β 3 adrenergic receptor (β 3AR). TH receptors, both α and β subunits, are expressed in BAT. Synergism between TH and SNS causes an effect via TR α , and the transcription of UCP1 is upregulated by TR β (7). In addition, increased tissue levels of T3 amplify the SNS effects, including UCP1 gene transcription.

The present study is focused on the following three genes: DIO2, UCP1, and β 3AR. These genes are key molecules in BAT thermogenesis. In fact, some studies have demonstrated that these genes are associated with the pathogenesis of adulthood obesity (8-11). However, few studies have reported the association between these genes and pediatric obesity. Therefore, we examined the effects of DIO2 Thr92Ala, UCP1-3826 A/G, and β 3AR Trp64Arg polymorphism on pediatric obesity.

Methods

Subjects

This study was approved by the institutional review board (IRB) of Kyoto Prefectural University of Medicine (IRB number: RBMR-G-71-7). According to Japanese guidelines, individuals with a percentage of overweight (POW) $\geq 20\%$ are classified as obese (12). POW, which is the modified weight-for-height method, is widely used as a surrogate marker of childhood obesity in Japan (13). POW is calculated using the following formula:

$$\text{POW (\%)} = 100 \times (\text{measured weight} - \text{standard weight}) / \text{standard weight}$$

Japanese standard weight is the age- and sex-specific weight for height, which is based on data from the Annual Report of School Health Statistics 2000 by the Ministry of Education, Culture, Sports, Science, and Technology, Japan. POW is reported to be a more appropriate method than BMI % for school-age children. A POW of 20% is equivalent to approximately the 90th BMI % of children with average height and weight, and the criteria for obesity are defined as POW $\geq 20\%$ ($\geq 120\%$ of the standard weight) (14). For non-obese children (NOB), study participants were recruited during an annual medical check-up at a junior high school in Kyoto. The NOB group did not include children with underlying conditions. Informed consent was obtained from 288 children and their parents. Eighteen children were excluded from the NOB group due to a high POW. These children were included in the obese children group (OB). Eventually, 270 children were enrolled in the NOB group. The median (range) age was 13.5 years (12.1-15.2). In the OB group, 68 obese children who visited our outpatient clinic were selected. Informed written consent of these children was obtained through their parents. Finally, we enrolled 86 children as OB (18 children as above were added to this group) (Fig 1). The median (range) age was 11.1 years (4.6-17.5) (Table 1). POW is unique to Japan; thus, the Rohrer index was used to verify that the same results could be obtained using global obesity standards. The presence or absence of obesity was determined using the Rohrer index, and the same analysis was performed. The Rohrer index was determined in kilograms per

cubic meter, and the criteria for obesity were defined as Rohrer's index ≥ 145 . Based on the Rohrer index, we classified 265 and 91 children into the NOB and OB groups, respectively (Table 2).

Genotyping

Genomic DNA was extracted from blood leukocytes using a genomic DNA separation kit (DnaQuick $\square$, DS Pharma Biomedical, Osaka, Japan). We analyzed the following polymorphisms of three genes; DIO2 Thr92Ala (rs225014), UCP1-3826 A/G (rs1800592), and β 3AR Trp64Arg (rs4994). Each gene was detected via polymerase chain reaction (PCR) using with the forward and reverse primers as follows: DIO2 forward primer = 5'-GGTACCATTGCCACTGTTGTCA-3', DIO2 reverse primer = 5'-GTCAGGTGAAATTGGGTGAGGAT-3', UCP1 forward primer = 5'-CCAGTGGTGGCTAATGAGAGAA-3', UCP1 reverse primer = 5'-GCACAAAGAAGAAGCAGAGAGG-3', β 3AR forward primer = 5'-CGCCCAATACCGCCAACAC-3', β 3AR reverse primer = 5'-CCACCAGGAGTCCCATCACC-3'.

Genotyping was performed by using ABI 7500 Fast Real-time PCR System (Applied Biosystems, Foster City, CA, USA), TaqMan[®]Genotyping PCR Master Mix (Thermo Fisher Scientific, Waltham, MA, USA), and TaqMan[®]SNP Genotyping Assay (Thermo Fisher Scientific).

Biochemical analysis

Clinical data were collected as follows: sex, age at first visit, height, weight, BMI, POW, serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL), Low-density lipoprotein cholesterol (LDL), triglycerides (TGs), random blood glucose (RBG), insulin, and hemoglobin A1c (HbA1c). Blood samples were randomly collected.

Statistical analysis

Clinical and laboratory data were summarized as median (P25-P75) for continuous variables and number (%) for categorical variables and compared between groups stratified according to obesity status (NOB, OB) and genotype prevalence using Mann-Whitney U test or Fisher's exact test. The association between DIO2/UCP1/ β 3AR genotypes and obesity was analyzed using cross tabulation and Fisher's exact test. Simple and multiple logistic regression analyses were performed to evaluate the contribution of gene polymorphism to obesity. For multiple logistic analysis, each genotype in each gene was included as an independent variable: DIO2 Thr/Thr, DIO2 Thr/Ala, DIO2 Ala/Ala, UCP1 AA, UCP1 AG, UCP1 GG, β 3AR Trp/Trp, β 3AR Trp/Arg, and β 3AR Arg/Arg. In multiple logistic analysis, a backward stepwise selection method was applied and the best-fit model was determined according to the Akaike information criterion. In this exploratory study, sample size was not determined statistically, and multiplicity adjustment was not considered in the statistical analysis. A P value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA).

Results

Clinical characteristics of the subjects

The clinical characteristics of the NOB and OB groups classified based on POW are shown in Table 1. The median age and height of the NOB group were higher than those of the OB group. For lipid profiles, TC, LDLC, and TG levels in the OB group were significantly higher than those of the NOB group, and the HDLC level in the NOB group was significantly higher than that of the OB group. For glucose metabolism parameters, RBG, insulin, and HbA1c levels in the OB group were significantly higher compared to those of the NOB group. Similar results were obtained from the obesity classification using Rohrer's index (Table 2).

Genotype distributions of SNPs

Genotype distributions of DIO2 Thr92Ala, UCP1 -3826 A/G, and β 3AR Trp64Arg in the NOB and OB groups are shown in Table 3. The prevalence of the homozygous Ala allele of DIO2 in the OB group is significantly higher than that of the NOB group on the Thr/Thr and Ala/Ala genotype ($P = 0.004$). The genotype distribution of UCP1-3826 A/G and β 3AR Trp64Arg did not significantly differ between the obese and non-obese groups ($P = 0.156$ and 0.793 , respectively). The outcomes of simple and multiple logistic analyses with respect to obesity are summarized in Table 4. DIO2 Ala/Ala was associated with obesity, with an odds ratio (OR) of 3.393 (95% CI 1.498-7.687, $P = 0.003$) via simple logistic analysis. In contrast, ORs of UCP1-3826 A/G and β 3AR Trp64Arg were 1.831 (95% CI, 0.955-3.512, $P = 0.069$) and 0.819 (95% CI, 0.263-2.555, $P = 0.731$), respectively. A simple logistic analysis of obesity classification was also performed based on Rohrer's index. The results also showed that DIO2 Ala/Ala was associated with obesity, which was classified based on Rohrer's index (OR of 3.149, 95% CI 1.396-7.103, $P = 0.006$) (Table 5). Multiple logistic analysis also showed that DIO2 Ala/Ala was significantly associated with obesity (Table 4). The percentage of correctly classified cases, sensitivity, and specificity of logistic analyses were 0.551 (0.497-0.603), 0.628, and 0.526, respectively.

Clinical characteristics of each SNP genotype

Table 6 shows the clinical characteristics of DIO2 Thr92Ala. BMI, POW, and insulin levels in the DIO2 Ala/Ala genotype were significantly higher than those in the DIO2 Thr/Thr ($P < 0.05$). However, insulin levels were not significantly different after adjusting for body weight. TC, LDLC, and HbA1c of the AG genotype were significantly higher than those of the AA genotype ($P < 0.05$). Interestingly, those of the GG genotype were not significantly different. β 3AR, BMI, and RBG of the Arg/Arg genotype were significantly lower than those of Trp/Trp (Supplemental Table 1).

Discussion

Obesity is a highly complex heterogeneous disease caused by multiple environmental, lifestyle, and genetic factors. Results from family and twin studies have suggested that genetic factors explain 40% to 70% of the inter-individual variation in obesity susceptibility (15). Individuals with pediatric obesity frequently remain obese in adulthood. It is important to elucidate the interaction between genetic factors and pediatric obesity, and to manage obesity in childhood. Recently, BAT has been identified as a novel target of obesity, as it increases energy expenditure by non-shivering thermogenesis. BAT-related gene

polymorphisms are associated with obesity (8-11). However, these relationships have not yet been fully elucidated, especially in pediatric obesity. Therefore, we carried out a case-control study to investigate the association of pediatric obesity with three SNPs (DIO2 Thr92Ala, UCP1-3826 A/G, β 3AR Trp64Arg) related to BAT. We demonstrated a significant correlation between the DIO2 Thr92Ala polymorphism and childhood obesity.

In the present case-control study, the frequency of the homozygous Ala allele of DIO2 was significantly higher in the OB than in the NOB group (15.1% vs. 6.3%, $P = 0.004$) (Table 2). These frequencies resulted in an OR of 3.393 (95% CI 1.498-7.687) for the DIO2 Ala/Ala genotype in the OB group (Table 3). More than 40% of subjects with DIO2 Ala/Ala were obese, which was the highest prevalence of obesity among all genotypes (Fig 2). This result is similar to that of a previous study showing that the DIO2 Ala/Ala genotype is strongly associated with obesity, concomitant with insulin resistance in a large cohort of patients with type 2 diabetes mellitus (8). Individuals with DIO2 Ala/Ala tend to have insulin resistance with a lower glucose disposal rate in adult obese Caucasians (11). There are three isoforms of DIO; DIO1, DIO2, and DIO3. DIO1 and DIO2 convert T4 to T3 by catalyzing 5'-deiodination, and DIO1 and DIO3 convert T4 to an inactive metabolite, rT3, by catalyzing 5-deiodination (16, 17). DIO2 exhibits a higher catalytic capacity than DIO1; thus, DIO2 plays a critical role in the production of T3 (18, 19). TH (T4 and T3) regulates metabolic processes, such as body weight, lipolysis, and thermogenesis (20). DIO2 Ala mutation impairs DIO2-mediated conversion of T4 to T3 in thyroid-deficient patients (7, 21-24), and DIO2 Ala mutation reduces intracellular conversion of T4 to T3 compared to DIO2 WT (23). Therefore, DIO2 Ala mutation could reduce the TH-mediated thermogenesis of BAT, leading to obesity. However, not all studies examining this genotype have verified the association with obesity, despite subjects having insulin resistance (25, 26). This discrepancy with the present study might be due to differences in age. In the present study, young individuals aged ≤ 18 years of age were enrolled. In contrast, all previous studies enrolled older people aged more than 40 years. BAT mass is highly present in infancy and declines in adulthood (27). Therefore, BAT might impact childhood more than adulthood. Furthermore, the activity of BAT increases during childhood, reaching its peak at approximately 12 years, and then declines during adulthood (28). The average age of children enrolled in the present study was 12 years. This concordance in age might have affected the results. We believe that adolescents approximately 12 years of age are suitable for assessing the association of obesity and gene polymorphisms related to BAT, because other factors, such as environmental, lifestyle, and genetic factors, are likely to be more involved in the pathogenesis of obesity in adulthood. In contrast, in adulthood, insulin resistance might be the main phenotype caused by DIO2 polymorphism. DIO2 is also expressed in skeletal muscles, and TH upregulates the expression of glucose transporter 4, which is responsible for glucose uptake. Therefore, skeletal muscle is the main glucose-consuming tissue. DIO2 polymorphism might lead to insulin resistance in adulthood, as skeletal muscle mass in adulthood is more abundant than in children. More importantly, there were no significant differences in insulin levels between DIO2 genotypes after adjusting for body weight. Higher insulin levels in the DIO2 Ala/Ala genotype might be secondary to obesity.

Previous studies have demonstrated that DIO2, UCP1, and β 3AR have a mutual impact on obesity in adulthood (10, 11). Therefore, the present study examined the gene-gene interaction of the DIO2 Thr92Ala

genotype with UCP1-3826 A/G and β 3AR Trp64Arg in pediatric obesity. The present study found no significant association between DIO2 Thr92Ala and UCP1-3826 A/G and β 3AR Trp64Ar in pediatric obesity. This discrepancy from studies investigating adult obesity might also be due to age. The combination of UCP1 and β 3AR polymorphisms is related to reduced BAT mass with age (29), suggesting that aging uncovers the effects of the gene combination on obesity. Further studies are needed to investigate the effect of UCP1 and/or the combination of DIO2 and UCP1 on pediatric obesity.

This is the first study reporting the association of DIO2 Thr92Ala polymorphism with pediatric obesity. The present study also suggests that BAT-related SNPs should be assessed in pediatric obesity. There are several limitations in the present study. 1) Due to its exploratory nature, the sample size was not determined on a statistical basis, and multiplicity of tests was not considered in statistical analysis. 2) There is difference in mean age between the NOB and OB groups. The mean height is expected to increase with age; the taller children are, the higher are their BMIs. 3) There is a lack of data on pubertal stage. Data on the pubertal stage are important for assessing insulin levels, as children physiologically develop insulin resistance and insulin levels increase with age, during puberty. The OB group had a higher insulin concentration, even though the median age in the OB group (11.1 years (9.1-13.8)) was younger than that in the NOB group (13.5 years (12.9-14.1)). Therefore, we believe that higher insulin levels in the DIO2 Ala/Ala genotype represent insulin resistance (30). 4) Puberty alters body composition differently according to sex. During puberty, boys gain only lean mass, but girls gain both lean mass and fat mass. Therefore, the effect of altered body composition during puberty due to a lack of data on the pubertal stage could not be assessed. 5) Some longitudinal studies have shown that girls have a significant decline in physical activity compared to boys during puberty (31, 32). This decline in physical activity due to sex difference during puberty might affect obesity. 6) Random glucose and insulin levels were examined in the present study. However, fasting glucose and insulin levels should also be examined to assess the insulin resistance. 7) Population-based non-obese children were included as controls in the present study. However, hospital-based non-obese children should have been enrolled as controls to match the background of all participants. Due to the various limitations of this study, further studies are needed to validate the results.

Conclusion

In conclusion, the results of this study indicate that the homozygous Ala/Ala allele of the DIO2 gene is associated with an increased risk of obesity in children. The present study also suggests that pediatric obesity might be suitable for assessing the association with gene polymorphisms related to BAT. These results indicate that it is important to assess DIO2 Thr92Ala polymorphism in pediatric obesity, and functional investigations are necessary to further elucidate the findings, e.g. infrared thermography.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Kyoto Prefectural University of Medicine. Written informed consent was obtained from each patient and their parents.

Consent for publication

Written informed consent for the publication of clinical details and images was obtained from the patient's parents. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and material

The datasets supporting the conclusions of this article are included within the article.

Competing interests

Each author declares that they have no competing interests.

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Authors' contributions

J.M., M.Y., S.M., Y.K., H.M., K.K., S.S., K.K., and H.N. attended to the patients; T.O., Y.T., K.S., S.F and K.K. performed the gene analysis; T.O., J.M., H.Y. and H.N. analyzed the data; T.O. and J.M. wrote the manuscript; J.M., K.K., H.N., and H.H. provided conceptual advice. All authors have read and approved the final manuscript.

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Tables

Due to technical limitations, table 1-6 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Flowchart for study data selection.

Figure 2

Correlation graph between all genotypes and the prevalence of obesity.

Supplementary Files

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