Correlates of the *FTO* Gene Variant (rs9939609) and Growth of American Indian Infants

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Aim: Obesity is a global, growing public-health problem. The detrimental health consequences of obesity are significant and include co-morbidities such as diabetes, coronary heart disease, and some types of cancer. To date, findings relating the A allele of the *FTO* variant rs9939609 to increased energy intake and risk for obesity have been fairly consistent across multiple populations. However, it is not known whether that relationship is also present in American Indian (AI) populations. The purpose of this study was to examine the minor allele frequency of the *FTO* variant rs9939609 and its associations with birth weight, weight for length (WFL) Z score, and amount of formula intake in AI infants. **Design:** A cross-sectional exploratory descriptive design was applied with a sample of 49 AI mother-infant dyads. **Results:** Mothers with an A allele had higher prepregnancy body mass index than those without an A allele, though difference was not statistically significant ($p=0.08$). Infants with an A allele tended to have higher birth weights, WFL Z score at age 14 to 20 weeks, and 24-h formula consumption compared with infants without an A-allele, though those differences were not statistically significant ($p>0.05$). Neither maternal nor infant A alleles were statistically significantly associated with birth weight, WFL Z score, and amount of formula intake in AI infants ($p>0.05$). **Conclusions:** The findings do not confirm the association of the A allele of the *FTO* variant rs9939609 with birth weight, amount of formula intake, and WFL Z score in AI infants.

Introduction

THE NUMBER OF U.S. children who are overweight and obese remains high. Approximately one third of children in the United States are overweight or obese (Ogden *et al.*, 2008). Among these children, significant racial-ethnic disparities are evident. For instance, American Indian (AI) children have the highest incidence of obesity of any ethnic group in the United States (Zephier *et al.*, 2006), and these children appear to develop obesity at an earlier age. Pediatric Nutrition Surveillance data demonstrated that 19.5% of AI infants aged 24–59 months were obese (body mass index [BMI] ≥ 95 th percentile) (Polhamus *et al.*, 2009). Although this indicates that early life exposures may be important in the development of obesity in AI children, limited research has been conducted in these children to identify the factors contributing to obesity development in early childhood.

Previous studies have identified a substantial genetic influence on individual BMI differences (Haworth *et al.*, 2008; Wardle *et al.*, 2008a). The fat mass and obesity-associated (*FTO*) gene was the first well-replicated genetic correlate of body weight and fat mass (Dina *et al.*, 2007; Frayling *et al.*,

2007; Scuteri *et al.*, 2007). Recent genome-wide association studies on European ancestries have identified that rs9939609, a common variant in the *FTO* gene, induces susceptibility to obesity in large populations of adults and children (Dina *et al.*, 2007; Scuteri *et al.*, 2007). The association of the *FTO* gene with an increased BMI has been confirmed in several studies across 14 populations (Dina *et al.*, 2007; Frayling *et al.*, 2007; Scuteri *et al.*, 2007; Hunt *et al.*, 2008). Specifically, the A allele of the variant rs9939609 in the *FTO* gene, located on chromosome 16, is associated with an increased risk for obesity development (Frayling *et al.*, 2007; Hinney *et al.*, 2007; Bauer *et al.*, 2009).

Note: The term “American Indian (AI)” is a preferred term and will be used throughout this article (Koerner, 2004; Brunner, 2007).

Studies have demonstrated that adult carriers of either single A or two A alleles had significantly higher BMI (weight [kg]/height² [m]) than individuals without the A allele. For example, European adults with one A allele had an odds ratio of 1.18 for being overweight and 1.31 for being obese compared with those without an A allele (Frayling *et al.*, 2007; Scuteri *et al.*, 2007). European children and adolescents

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between 7 and 14 years of age with one A allele had an odds ratio of 1.27 for being overweight and 1.35 for being obese compared with those who had no A allele (Frayling *et al.*, 2007). In addition, the z-score for BMI of children with one A allele has a wider variation, from 0.05 to 0.5 kg/m², than did those with no A allele (Frayling *et al.*, 2007). A twin study revealed that 10-year-old Caucasian twins with two A alleles had a mean BMI 0.73 points higher than twins without an A allele (Wardle *et al.*, 2008a). Further, a study of 234 full-term, healthy Caucasian newborns demonstrated that newborns with two A alleles (AA) had 17% to 20% higher total, truncal, and abdominal fat mass at age 2 weeks compared with those without an A allele; these differences remained unchanged after controlling for types of feeding (Lopez-Bermejo *et al.*, 2008). However, the effects of the A allele of the variant rs9939609 on birth weight and later weight for length (WFL) Z score in AI children has not been investigated.

The *FTO* gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase that is present in several tissues but is most plentiful in the hypothalamus, the control center for energy balance (Gerken *et al.*, 2007). In animal studies, the *FTO* messenger ribonucleic acid levels are regulated by feeding and fasting, suggesting a potential role for this gene in central control of energy homeostasis and providing a mechanistic link between the *FTO* and body weight and energy homeostasis (Gerken *et al.*, 2007). Evidence supporting a similar connection in humans has also been reported. A twin study of 214 UK families indicated that children with two A alleles of the *FTO* rs9939609 had significantly higher caloric intake than children without an A allele ($p < 0.05$) (Wardle *et al.*, 2008b). Further, a study of 289 children, aged 6 to 19 years, reported that children with at least one A allele of the *FTO* rs9939609 consumed a greater percentage of energy from fat ($p < 0.01$) and reported more frequent loss-of-control eating episodes ($p = 0.002$) compared with children without the A allele (Tanofsky-Kraff *et al.*, 2009).

Energy regulation is complex and multi-factorial, and the *FTO* gene is one of several potential contributors that have been reported to confer a risk for obesity through increased energy intake (Wardle *et al.*, 2008b; Tanofsky-Kraff *et al.*, 2009). Though the prevalence of obesity in AI children continues to rise, and is becoming one of the most serious public health problems facing AI children and adolescents, genetic contributors to this increase in general and specifically the frequency and potential contribution to energy intake of the A allele variant rs9939609 in the *FTO* gene in AI children remain unknown.

The purpose of this pilot study was to answer the following questions: (1) What is the Minor Allele Frequency (MAF), deviation from Hardy-Weinberg equilibrium, and linkage disequilibrium (reported as r^2) for the variant rs9939609 in the *FTO* gene of AI infants and mothers? (2) Are there differences in mean BMI between AI mothers of infants aged between 14 and 20 weeks, with and without an A allele? and 3) Are there differences in mean birth weight, WFL Z scores, and amount of formula intake at age 14–20 weeks between AI infants with and without an A allele? Figure 1 depicts the theoretical framework for the study. Measuring WFL reflects adiposity and future obesity risk better than does weight alone (Benn, 1971). According to previous research, presence of the A allele of the variant rs9939609 in the *FTO* gene is associated with body weight, fat mass, and energy intake (Dina *et al.*, 2007;

Frayling *et al.*, 2007; Wardle *et al.*, 2008b, 2009). However, there is as yet no evidence to support these associations in the AI population. Thus, the associations among the variant rs9939609 in the *FTO* gene, infant birth weight, and amount of milk intake per day and infant WFL Z score at age between 14 and 20 weeks were examined in this study. Potential covariates that may influence infant growth, including infant age and gender, maternal age, education, income, and pre-pregnancy BMI, were also evaluated.

Methods

Design and setting

This pilot study employed an exploratory descriptive design with a total of 49 AI mother-infant dyads who received healthcare services from an Indian hospital-based outpatient clinic in North Dakota. Inclusion criteria were (1) self-identified as AI ancestry; (2) mothers had a full-term (newborn gestational age assessment documented in the health record > 37 weeks) singleton infant aged 14 to 20 weeks; (3) infants did not have any health problems that would affect their feeding; (4) neither mother nor infant had any congenital anomalies; (5) infants were either exclusively formula-fed (never breastfed) or partially breastfed during the first month of life; and (6) mother spoke English (for communication during participation).

IRB approval was obtained from the researcher's university review board and the Indian Health Services Institutional Review Board. Approval was also obtained from the Tribal Council. Confidentiality was guaranteed, with all findings reported in group format. The medical records of infants who were born at or received healthcare services from an Indian hospital in the Great Northern Plains were reviewed to determine eligibility. Mothers of eligible infants were contacted by telephone or in-person contact during clinic visits. Written informed consent and authorization to review medical records were obtained from mothers before participation in the study. A total of \$25 grocery gift certificate was given to mothers who completed the study to compensate them for their time.

Participants

Of the 76 eligible mother-infant dyads, 49 (64.5%) agreed to participate and completed the study. The means $\pm$ standard deviation for ages of these mothers and infants were 25 ± 5 years and 16 ± 2 weeks, respectively. About half (49%) of mothers had completed high school, and two thirds (63.3%)

FIG. 1. Theoretical framework.

had an annual family income of <\$20,000. Most of them had never married (61.2%), and 53% used tobacco. Medical records and lab results were used to identify any exclusionary conditions. Only two mothers reported gestational diabetes, and neither were prescribed medications. The mean maternal prepregnancy BMI was 28.4 ± 8.2 . Gestational age ranged between 37 and 42 weeks.

All of the infants met the inclusion criteria. Of 49 infants, 57.1% were boys. The mean birth weights and lengths of infants were 7.5 ± 1.0 lb. and 20.7 ± 3.4 in., respectively. At birth, one third of the infants had WFL percentiles between the 50th and 84th percentile (35.6%), and 25.5% were between the 85th and 94th percentile. None were at the 95th percentile or above. At ages 14 to 20 weeks, WFL percentiles were between the 85th and 94th percentile for 20.3% of infants, and at the 95th percentile or higher were 11.2%. The mean WFL Z scores at birth and between 14 and 20 weeks of age were -0.97 ± 1.5 and 0.05 ± 2.2 , respectively. The mean total milk intake per day at age 14 to 20 weeks was 34 ± 8.3 fluid oz.

Procedures

Mothers and their 14- to 20-week-old infants met with the researcher at a pediatric clinic of the Indian hospital after their clinic visit or later at a special appointment with the researcher. Data on infants' birth weight and length, gestational age, and date of birth were extracted from medical records. Infant current weight and length were also measured by the researcher using a hospital infant measuring board following the standard protocol (NHANES III, 1988). Infants were weighed to the nearest 10 g or 1/2 oz, without shoes and wearing light underclothing or diaper. Infants wearing wet diapers had their diapers changed before measuring their weight. To measure recumbent length, the infant was placed supine on the infant measuring board. The infant's head contacted the fixed headboard. The researcher placed one hand gently but firmly over the knees to prevent the knees from flexing, with the infant's toes pointing directly upward, and another hand pulled the movable footboard to rest firmly against the infant's heels. The measurement was recorded to the nearest 0.1 cm. The mean z-score for WFL was calculated using the Epi Info (TM) program, version 3.5.1 (www.cdc.gov/epiinfo/CDC).

Mothers were asked to complete a self-administered demographic questionnaire and collect their own saliva (for genotyping of the selected variant in the *FTO* gene) using a DNA self-collection kit (DNA Genotek, Inc.) that included instructions. In addition, mothers were asked to complete an infant feeding questionnaire (data are not reported in this paper) and a take-home 24-h formula intake survey. The infants' saliva was collected from their cheek pouch (buccal) by the researcher using infant saliva sponges and the DNA Self-Collection Kit.

FTO genotyping

A predesigned "TaqMan" (Applied Biosystems, Inc.) genotyping assay and protocol was implemented for the selected variant, rs9939609, on a real-time, Mini-Opticon (Bio-Rad Laboratories, Inc.), 4-color thermocycler. Controls representing each of the three possible genotypes and a "blank, no template" control were included with each analytic run. Controls for the heterozygotes and homozygous T allele were

obtained from the Coriell Institute for Medical Research, and the genotypes were confirmed at the HapMap (Haplotype Map of the Human Genome) website (<http://hapmap.ncbi.nlm.nih.gov>) and on each of an additional 13 runs. The control for the homozygous A genotype was discovered among the samples collected and confirmed on each of an additional 12 runs (The International HapMap Consortium, 2005). Genotyping was robust, with no samples completely failing analysis among the 98 samples collected. Among the 98 samples, no instances of conflicting genotypes were found on repeat testing of the same sample. Maternal-infant incompatibilities were also not shown.

Data analysis

Descriptive statistics appropriate for measurement level (i.e., mean, median, standard deviation, skewness, kurtosis, frequencies, and stem-and-leaf plots) were examined for all variables, using the Predictive Analytics SoftWare version 17.0. Conformance to statistical assumptions was examined for all inferential tests, and no violations were found. The relationships between demographics and all other study variables were tested. The MAF for the variant rs9939609 in the *FTO* gene were estimated using Haploview (Barrett *et al.*, 2005; Wigginton *et al.*, 2005). General Linear Model (GLM) univariate was used to analyze the differences in mean BMIs of the mothers with an A allele and without an A allele. Mean birth weight, WFL Z scores, and amount of milk intake at age between 14 and 20 weeks of the infants who carried A allele and non-A allele were also analyzed using GLM univariate. The potential covariates (infant age and gender, maternal age, maternal prepregnancy BMI, education, and family income) were included as appropriate. Since the homozygous A genotype (AA) was found in only one participant of each mother and infant groups, only two allele states could be used in the analyses, namely A allele present; A allele absent.

Subsequent analyses were performed to compare differences in mean birth weight, WFL Z scores, and amount of milk intake at age between 14 and 20 weeks among four subgroups of infants (+A infant/+A mother vs. +A infant/-A mother vs. -A infant/=A mother vs. -A infant/-A mother) using the two-by-two GLM analyses. The effects of maternal and infant *FTO* genotypes and their interaction effects on infant birth weight, WFL Z scores, and amount of milk intake at age between 14 and 20 weeks were also analyzed. An infant with homozygous A genotype (AA) was excluded in the subsequent analyses to reduce a confounding effect of two A alleles.

Results

Description of participants

Sample characteristics for female and male infants are provided in Table 1. Male and female infants tended to have similar means for age, birth weight, birth and 14–20 week WFL Z score, and proportion having an *FTO* A allele (all $p > 0.05$). However, male infants had greater mean 24-h formula intake (37.2 oz.) than female infants (31.5 oz, $p = 0.04$). Associations between infant growth outcome variables (weight and length at birth and at 14 to 20 weeks old, as well as WFL Z score at birth and at 14 to 20 weeks old) and potential covariates (infant age and gender, maternal age,

TABLE 1. SAMPLE CHARACTERISTICS BETWEEN FEMALE AND MALE INFANTS

Infant characteristics	Female (n=21) Mean $\pm$ SD	Male (n=28) Mean $\pm$ SD	p
Age (weeks)	15.0 $\pm$ 1.72	15.6 $\pm$ 2.5	0.33
Birth weight (lbs)	7.41 $\pm$ 1.03	7.52 $\pm$ 0.86	0.67
Birth WFL Z score	0.36 $\pm$ 0.27	0.42 $\pm$ 0.29	0.60
WFL Z score at 14–20 weeks old	0.59 $\pm$ 0.29	0.67 $\pm$ 0.31	0.67
24-h formula intake (fluid oz)	31.47 $\pm$ 5.49	37.16 $\pm$ 6.20	0.04 ^a
A allele present, proportion $\pm$ SD	0.57 $\pm$ 0.50	0.32 $\pm$ 0.47	0.15

^a $p < 0.05$.

WFL, weight for length.

maternal prepregnancy BMI, education, and family income) were examined to identify covariates to be controlled. Infant age was positively correlated with infant weight at age 14 to 20 weeks ($r = 0.47$, $p = 0.001$). Family income was positively associated with infant birth weight ($r = 0.31$, $p = 0.02$) and WFL Z score ($r = 0.40$, $p < 0.01$); however, these relationships disappeared at age between 14 and 20 weeks. Maternal education was positively associated with infant WFL Z score at birth ($r = 0.39$, $p < 0.01$). Maternal prepregnancy BMI was not associated with infant weight and height either at birth or at age between 14 and 20 weeks ($p > 0.05$). Neither maternal nor infant *FTO* genotypes were associated with any potential covariates.

Allele frequency

The allele frequencies of the *FTO* variant rs9939609 for both mothers and infants are shown in Table 2. The frequency of the minor A allele was 26.5% for mothers and 22.4% for infants; they were in Hardy–Weinberg equilibrium ($p > 0.07$ and $p = 0.23$, respectively), indicating that the *FTO* allele frequencies in this population are not changing over time (Hartl and Clark, 1997).

Differences in mean BMIs of mothers with different genotypes

The mean BMIs between mothers with and without an A allele were compared and are shown in Table 3. Although there was no statistically significant difference in mean BMI ($p = 0.08$), mothers without an A allele were, on average, overweight (Mean = 26.3), whereas mothers with an A allele were, on average, obese (Mean = 30.4).

TABLE 2. *FTO* GENOTYPE FREQUENCIES AND THE FREQUENCY OF THE A ALLELE IN MOTHER AND INFANT SAMPLES

Genotypes n=98					
	TT	AT	AA	A-allele frequency (%)	95% CI
Mothers	24	24	1	26.5	0.265 $\pm$ 0.087
Infants	28	20	1	22.4	0.224 $\pm$ 0.083

AA, homozygous carriers of the A allele; AT, heterozygous carriers; TT, noncarriers; CI, confidence interval.

TABLE 3. MEAN $\pm$ STANDARD DEVIATION FOR BODY MASS INDEX OF MOTHERS WITH AN A ALLELE AND WITHOUT AN A ALLELE

	Genotype		P
	TT (n=24)	AT & AA (n=25)	
Mom BMI (kg/m ²)	26.3 $\pm$ 7.3	30.4 $\pm$ 8.7	0.08

BMI, body mass index.

Differences in mean birth weight, WFL Z score at birth and at age between 14 and 20 weeks, and amount of 24-h formula intake between infants with different genotypes

Although bivariate associations involving infant sex and age were observed, no statistically significant interaction or main effects for either infant sex or infant age were identified within the GLM models examined (all $p > 0.05$), and they were eliminated from consideration as covariates. Bivariate (*t*-test) results comparing genotype group means for these variables appear in Table 4. Infants with an A allele tended to have higher birth weights, WFL Z score at age 14 to 20 weeks, and 24-h formula consumption compared with infants without an A-allele; however, the differences were not statistically significant ($p > 0.05$).

Differences in mean birth weight, WFL Z score, and amount of 24-h formula intake at age between 14 and 20 weeks between infants with different maternal genotypes

The mean birth weight, WFL Z score, and amount of 24-h formula intake at age between 14 and 20 weeks among four subgroups of infants were compared and are shown in Table 5. A group of A allele infants with A allele mothers had the highest mean birth weight, WFL Z score, and 24-h formula intake at age 14 to 20 weeks among four groups of infants. A group of A allele infants with non A-allele mothers tended to have higher mean birth weight, WFL Z score, and 24-h formula intake at age between 14 and 20 weeks compared with non A-allele infant groups. A group of non A-allele infants with non A-allele mothers had the lowest mean birth weight, WFL Z score, and 24-h formula intake at age between 14 and 20 weeks among four groups of infants. Neither infant nor maternal A alleles were statistically significantly associated

TABLE 4. MEAN $\pm$ SD FOR AGE, BIRTH WEIGHT, WEIGHT FOR LENGTH Z SCORE, AND 24 H FORMULA INTAKE BETWEEN INFANTS WITH AN A ALLELE AND WITHOUT AN A ALLELE

	Genotype		p
	TT (n=28)	AT & AA (n=21)	
Age (weeks)	14.8 $\pm$ 2.0	15.5 $\pm$ 2.3	0.26
Birth weight (lbs)	7.4 $\pm$ 1.0	7.6 $\pm$ 0.8	0.41
WFL Z score at birth	0.4 $\pm$ 1.3	0.4 $\pm$ 1.7	0.67
WFL Z score aged between 14 and 20 weeks	0.7 $\pm$ 2.3	0.8 $\pm$ 2.2	0.55
24-h formula intake (fluid oz)	32.2 $\pm$ 5.3	36.6 $\pm$ 6.6	0.06

TABLE 5. MEAN $\pm$ SD FOR BIRTH WEIGHT, WEIGHT FOR LENGTH Z SCORE, AND 24 H FORMULA INTAKE BETWEEN INFANTS WITH PRESENCE AND ABSENCE OF A MATERNAL A ALLELE

Maternal A Allele	Infant A Allele	
	Present n=20	Absent n=28
Present (n=24)		
n (%)	13 (25.5%)	11 (23.4%)
Birth Weight (Lbs)	7.7 $\pm$ 0.7	7.5 $\pm$ 0.6
WFL Z Score (14–20 weeks old)	0.7 $\pm$ 2.2	0.4 $\pm$ 1.6
24-h Formula Intake (fluid oz.)	37.1 $\pm$ 3.9	32.8 $\pm$ 6.1
Absent (n=24)		
n (%)	7 (14.9%)	17 (36.2%)
Birth Weight (Lbs)	7.6 $\pm$ 0.7	7.3 $\pm$ 0.9
WFL Z Score (14–20 weeks old)	0.6 $\pm$ 1.7	0.2 $\pm$ 1.4
24-h Formula Intake (fluid oz.)	33.0 $\pm$ 3.2	32.0 $\pm$ 6.0

with birth weight, WFL Z score, and 24-h formula intake ($p > 0.05$). There was no evidence of interaction and main effects for infant and maternal A alleles on birth weight, WFL Z score, and amount of 24-h formula intake at age 14 to 20 weeks within the GLM models examined ($p > 0.05$, Table 6).

Discussion

The effect of the *FTO* gene variant on obesity is substantial in European adults and children. Adult Europeans who are homozygous for the risk-conferring variant rs9939609 A allele had a 1.67-fold higher odds ratio for obesity compared with those without a risk allele (Frayling *et al.*, 2007). However, since few studies have been done in AI populations, it is not known whether that relationship is also present in AIs. The proposed study is, to our knowledge, one of the first genetic studies to investigate the MAF of the *FTO* variant rs9939609 and its associations with birth weight, formula intake, and growth at age 14 to 20 weeks in AI infants.

MAF for the *FTO* variant rs9939609 in AI mothers and infants was 26.5% and 22.4%, respectively, which was considerably lower than in some Caucasian groups (39%) (Frayling *et al.*, 2007); however, the MAF in AI was similar to that reported in a Mexican population (20.4%–21.1%) (Villalobos-Comparán *et al.*, 2008). Since the MAF for the A allele for these groups is lower than in Caucasians, and since both AI and Mexican populations have higher risk for obesity than Caucasians, environmental factors such as types and amount of food intake and lifestyle patterns, along with the influence of

other weight-related genes and gene-environment interactions, may overshadow the A allele effects.

Although this study's findings indicated that AI mothers with an A allele had higher mean prepregnancy BMI than those without an A allele, there was no statistically significant difference ($p = 0.08$). It is not known whether that relationship is present in AI women, because few studies have been done in AIs; therefore, comparison with previous findings in terms of direction and magnitude is unavailable. A lack of statistical significance may be a result of insufficient power, and that effect size for the A allele is perhaps reduced in this population compared with Caucasians due to greater contributions from other genes, environment, and cultural practices.

The findings revealed that an A allele in the *FTO* gene was not significantly associated with infant birth weight and WFL Z score at birth and at age 14 to 20 weeks. The presence and absence of the A allele in infants or mothers did not influence infant birth weight and WFL Z score. There was no convincing evidence for modification by maternal A allele. This is consistent with previous research conducted in European and native African children finding that children with and without an A allele did not differ in birth weight (Frayling *et al.*, 2007; Jess *et al.*, 2008; Lopez-Bermejo *et al.*, 2008; Hennig *et al.*, 2009). Coupled with the finding by Jacobson *et al.* (2008), who reported that a difference showed up between one and three years in European population, a longer time period of growth might be necessary before effects of the A allele on WFL Z score become discernible in AI infants.

Although results indicated that AI infants with an A allele consumed statistically similar amounts of formula than those without an A allele ($p = 0.06$), in absolute terms, mean formula intake for AI infants with an A allele was greater than for infants without an A allele. In addition, a group of A allele infants with A allele mothers had the highest mean formula intake among four groups of infants. The direction of the difference is consistent with previous studies in terms of the potential contribution of the A allele to amount of energy intake (Cecil *et al.*, 2008; Timpson *et al.*, 2008; Wardle *et al.*, 2008b; Tanofsky-Kraff *et al.*, 2009). However, additional validation with larger sample sizes, which have more statistical power to detect an association with the A allele, and multiple long-term measures of formula consumption are needed.

In conclusion, our analyses were not able to determine the significant associations between the A allele and studied variables. Lack of discrepancy in observation of the relationships could be because there is a small number of the highest-risk homozygous AA allele, only observed in one infant and one mother. Most previous analyses were done in two A

TABLE 6. MAIN AND INTERACTION EFFECTS FOR INFANT AND MATERNAL A ALLELES ON BIRTH WEIGHT, WEIGHT FOR LENGTH Z SCORE, AND 24-H FORMULA INTAKE

	Infant A allele (IA)		Maternal A allele (MA)		IA * MA	
	Main effect		Main effect		Interaction effect	
	F	p	F	P	F	p
Birth weight ^a	0.52	0.45	0.07	0.78	0.21	0.64
WFL Z score ^a age between 14 and 20 weeks	0.27	0.60	0.71	0.40	0.03	0.91
24-h Formula Intake ^a	3.23	0.08	2.54	0.12	3.35	0.07

^aDegree of freedom (df) = 1.

alleles (homozygous) subjects with larger sample sizes that had more statistical power. Further, the impacts of gene-gene and gene-environment interactions could obscure the effect of the A allele in this population. An epigenetic event early in life influencing the development of obesity is very dynamic and remains fairly rudimentary. Our analyses were unable to suggest epigenetic influences on the growth of AI infants. Further investigation of the epigenetic effects in large mother-child pairs design that jointly models gene-environment interactions on maternal and newborn outcomes (Wang *et al.*, 2010) may lead to greater power to detect gene-environment interactions. The contribution of the A allele in predisposing to obesity in AI infants warrants additional studies.

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