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Variation in the fat mass and obesity related (FTO) genotype is not associated with body fatness in infants, but possibly with their length.

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Abbreviations: BMI, body mass index; FFM, fat free mass; FM, fat mass; FTO fat mass and obesity; PATHOS, Parents And Their Offspring Study

Key words: body composition, fat mass, FTO, infant

Running title: FTO vs. infant size and body composition

Abstract

Background: Data relating variation at the fat mass and obesity related (FTO) locus (rs9939609) to fat mass in infancy are inconclusive.

Objective: To study relationships between FTO-genotype and infant size (at 1 and 12 weeks and at 1 year of age) and body composition (at 1 and 12 weeks).

Methods: Body composition was assessed using air displacement plethysmography in 207 infants. FTO was genotyped using the TaqMan assay.

Results: The number of risk alleles was related to length at 1 and 12 weeks ($P=0.007-0.033$) but not to fat mass. The relationship to length was stronger in boys than in girls.

Conclusions: Our results suggest that the FTO-genotype is not related during infancy to fat mass but is related to length in boys but not in girls.

Introduction

Obesity is influenced by genetics (1), and variation at the fat mass and obesity related locus (FTO) is related to body mass index (BMI) and fat mass (FM) in children and adults (2,3). In these studies addition of each risk allele at the single nucleotide polymorphism, rs9939609, was associated with a higher BMI or with more FM. Several studies report no such relationship in infants (4-6), and Sovio et al. even found an inverse association between the FTO-genotype and BMI below 2.5 years of age (7). In infancy, when BMI is a poor predictor of FM (8), studies relating the FTO-genotype to body composition are more relevant, but few such studies have been published. However, López-Bermejo et al. (9) reported a positive relationship between the number of risk alleles and FM in 2-week-old infants, while Mook-Kanamori et al. (6) found no such relationship at 6 months. In this longitudinal study, our aims were to relate the FTO-genotype to body size and composition in infants aged 1 and 12 weeks and to their weight and length at 1 year of age.

Methods

Healthy, singleton and full term (≥ 37 gestational weeks) infants of healthy mothers participated in PATHOS (Parents And Their Offspring Study). Parents (>90 % Caucasians) were recruited from a well-educated Swedish population between 2008 and 2010. Overweight and obesity were present in 21 % and 43 % of mothers and fathers, respectively. Infant size and body composition, assessed using air displacement plethysmography (8), were measured at 1 and 12 weeks of age. Parents reported weight and length of their 1-year-old infants after visiting a health clinic. Mode of feeding and parity were recorded. Gestational age was based on an ultrasound examination (10). The Regional Ethics Committee, Linköping, Sweden, approved the study and parents gave informed consent. Saliva was collected from infants and DNA was extracted using QuickExtract DNA Extraction Solution 1.0 (Epicentre

Biotechnologies, Madison, WI, USA). Genotyping, i.e. assessing the number of risk (A) or wild type (T) alleles at the FTO locus rs9939609, was based on real-time PCR (polymerase chain reaction) using the TaqMan Genotyping Assay (ID: C__30090620_10) and was analysed on a ABI Prism 7900HT “Sequence Detection System” (Applied Biosystems, Carlsbad, CA, USA). Call rate was 99% (207/209). Regression analysis (11) was used assuming an additive effect of FTO. Reported models were adjusted for maternal parity, infant sex, gestational age at birth and age at measurement. A previous study (12) suggested that the sexes respond differently to the FTO-genotype. Therefore, an interaction term (FTO x sex) was entered in the regression models. Values are means and standard deviations (SD). All hypothesis tests were two-sided and significance was accepted when $P < 0.05$. Statistical analysis was conducted using PASW Statistics 18 (IBM, Sowers, NY, USA).

Results and Discussion

Table 1 shows infant characteristics. **Table 2** shows relationships between the FTO-genotype, on the one hand, and infant size and body composition on the other hand. No significant relationships were found for BMI or FM. Additional adjustment for maternal BMI before pregnancy had minor effects on the results (data not shown). Our findings disagree with data reported by López-Bermejo et al. (9), but are in agreement with results reported by Mook-Kanamori et al. (6). These studies (6,9) assessed body composition using dual x-ray absorptiometry, a method requiring careful standardization. The number of risk alleles was positively related ($P < 0.05$) to fat free mass and weight at 1 and 12 weeks of age. However, these relationships were not significant when adjusted for infant length, suggesting that these observed effects can be explained by an effect on length. Thus we found a positive relationship between the number of risk alleles and length at 1 ($P = 0.033$) and 12 ($P = 0.007$) weeks but not at 1 year of age ($P = 0.052$). Earlier studies reported no such relationships (6,9)

but one study (13), which used a risk score based on several obesity associated loci including FTO (rs9939609), showed this score to be associated with length at 6 weeks of age.

The interaction term (FTO x sex) was significant ($P=0.047$) when length at 12 weeks was the dependent variable (Table 2). The corresponding interactions were weaker at 1 week ($P=0.067$) and 1 year ($P=0.11$) of age. However, these interactions were significant in unadjusted models ($P=0.024-0.048$). Furthermore, for boys, but not for girls ($P=0.59-0.98$), the number of risk alleles was positively related to length at the age of 1 week ($P=0.004$), 12 weeks ($P=0.001$) and 1 year ($P=0.012$).

Strengths of this study include accurate body composition data (14) and that results were adjusted for relevant confounders (8,15-17). Our sample size is similar to previous studies (6,9) but small for this kind of study, which is our main limitation. Furthermore, we cannot exclude that antenatal confounding by maternal genotype has affected our results. Obviously, our findings regarding a relationship between FTO-genotype and length of infant boys need confirmation. We encourage researchers to investigate this relationship since accelerated growth in infancy is a risk factor for later obesity (18).

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Table 1. Characteristics of girls* and boys† in the study at 1 and 12 weeks as well as at 1 year of age.

	1 week of age		12 weeks of age		1 year of age	
	Girls (n=97)	Boys (n=110)	Girls (n=97)	Boys (n=110)	Girls (n=96)	Boys (n=109)
Age (week)	1.0±0.3	1.1±0.3	12.1±0.4	12.1±0.4	53.1±2.4	52.7±2.1
Length (cm)	51.0±1.5	52.0±2.0	60.5±2.0	62.0±2.0	75.5±2.5‡	77.0±2.5‡
Length-for-age z-score [§]	0.24±1.12	0.15±1.11	0.32±0.97	0.27±1.12	0.31±0.95	0.45±0.94
Weight (g)	3515±438	3682±497	5856±573	6427±858	9700±940‡	10580±1070‡
Weight-for-age z-score [§]	-0.15±0.99	-0.15±1.09	-0.20±0.87	0.13±1.17	-0.14±0.98	0.11±1.07
BMI (kg/m ²)	13.4±1.1	13.6±1.2	15.9±1.1	16.8±1.7	17.0±1.3‡	17.7±1.4‡
FFM (g)	3042±312	3245±339¶	4263±364	4750±463¶	-	-
FM (g)	473±172	411±190¶	1593±356	1623±440¶	-	-
FM (%)	13.2±3.6	10.9±4.1¶	27.0±4.2	25.2±4.5¶	-	-
Any breastfeeding (%) (n)	100 (97)	100 (110)	96.9 (94)	96.4 (106)	-	-

Continued...

Table 1, continued.

Mean±SD. BMI, body mass index; FFM, fat free mass; FM, fat mass.

* Girls were born after 40.0±1.2 gestational weeks. They weighed 3530±450 g at birth, 33.0% (n=32) had no risk allele (TT), 45.4% (n=44) had one risk allele (AT), and 21.6 % (n=21) had two risk alleles (AA) for FTO (rs9939609). These frequencies were in Hardy-Weinberg equilibrium ($P=0.73$).

† Boys were born after 40.1±1.2 gestational weeks. They weighed 3680±490 g at birth, 38.2% (n=42) had no risk allele (TT), 44.5% (n=49) had one risk allele (AT), and 17.3 % (n=19) had two risk alleles (AA) for FTO (rs9939609). These frequencies were in Hardy-Weinberg equilibrium ($P=0.53$).

‡ Reported by parents after a visit to a health clinic.

§ Calculated using Swedish reference data (16).

¶ n=108.

Table 2. Results of regression analysis relating the number of FTO (rs9939609) risk alleles (0, 1 or 2) as independent variable to body size and composition (dependent variables) for 207 infants at 1 and 12 weeks as well as at 1 year of age.

Dependent variable	1 week of age*				12 weeks of age*				1 year of age*			
	n	b	r ²	P	n	b	r ²	P	n	b	r ²	P
Length [†] (cm)	207	0.31	0.023	0.033 [‡]	207	0.47	0.036	0.007 [‡]	205	0.41	0.019	0.052 [‡]
Girls	97	0.01	0.000	0.98	97	0.08	0.001	0.76	96	0.04	0.000	0.90
Boys	110	0.56	0.078	0.004	110	0.77	0.096	0.001	109	0.73	0.059	0.012
Weight [†] (g)	207	93.3	0.030	0.014 [§]	207	149.3	0.023	0.033 [§]	205	0.22	0.024	0.028 [§]
BMI (kg/m ²)	207	0.18	0.016	0.071	207	0.14	0.005	0.32	205	0.18	0.009	0.17
FFM (g)	205	56.4	0.022	0.036 [§]	205	103.3	0.034	0.008 [§]				
FM (g)	205	22.7	0.010	0.16	205	8.1	0.000	0.83				
FM (%)	205	0.36	0.005	0.31	205	-0.23	0.002	0.57				

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Table 2, continued.

b, slope of regression line (effect per risk allele); r^2 , coefficient of determination calculated from partial r ; P , P -value; BMI, body mass index; FFM, fat free mass; FM, fat mass.

* FTO was coded as: 0, no risk allele; 1, one risk allele; 2, two risk alleles. Thus the regression analysis assumed an additive effect of the number of risk alleles. Models were adjusted for maternal parity, infant gestational age at birth, infant age at measurement and infant sex (except when the sexes are analyzed separately).

† Length and weight at the age of 1 year were reported by parents after a visit to a health clinic.

‡ P for sex-interaction (i.e. number of FTO, rs 9939609, risk alleles x sex) was 0.067 (1 wk), 0.047 (12 wk), 0.11 (1 y). Furthermore, when including a sex-interaction (together with infant sex) in unadjusted models the corresponding P -values were: 0.026 (1 wk), 0.024 (12 wk), 0.048 (1 y).

§ Not significant ($P \geq 0.19$) when adjusted for infant length.

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