FTO rs9939609 polymorphism is associated with the presence of obstructive sleep apnoea in overweight and obese youth.

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Introduction

Emerging evidence suggests FTO polymorphisms are associated with obesity-related comorbidities including type 2 diabetes (T2DM), hypertension (HTN) and polycystic ovarian syndrome (PCOS). However association of FTO with other comorbidities such as obstructive sleep apnoea (OSA) in paediatric populations is less clear.

We aimed to investigate the prevalence of obesity-related comorbidities according to FTO genotype in an overweight and obese paediatric cohort.

Methods

Data were collected from patients recruited by the COBRA study who attended the weight management service at The Royal Children's Hospital (Melbourne). Comorbidities assessed were; 1 impaired glucose tolerance/ T2DM, 2 HTN, 3 hyperlipidaemia, 4 non-alcoholic fatty liver disease 5 OSA, 6 mental health issues, 7 eating disorders, 8 orthopaedic and 9 neurological disorders (**Table 2**). A cumulative binary comorbidity score of risk factors was assigned (range:1-9) to assess additive risk. Genotype (FTO rs9939609 SNP alleles; Sequenom MassARRAY MALDI-TOF MS), activity levels (Actical© accelerometry) and dietary consumption (Australian Food Frequency Questionnaire), were measured and collected. Body composition was measured with bioimpedance (Tanita BC-418). *Data were statistically analysed using chi-squared, one-way ANOVA and logistic regression as appropriate.*

Results

Patient demographics (n=197) were summarised below (**Table 1**). The minor allele frequency was 0.48. We did not observe any differences in characteristic variables between FTO genotype groups.

Table 1. Characteristics of the participant population.

	All M (SD) or N (%)	AA (n=45)	AT (n=100)	TT (n=52)	p
Anthropometry (n)					
Male	91 (46)	22 (49%)	45 (45%)	24 (46%)	0.91
Age# (197)	10.8 (3.5)	11.1 (3.5)	10.6 (3.6)	10.7 (3.4)	0.75
Peri/postpubertal	109	25	54	30	0.97
BMI-Z (197)	2.44 (0.44)	2.46 (0.36)	2.44 (0.58)	2.44 (0.42)	0.97
WHtR (171)	0.66 (0.11)	0.66 (0.14)	0.65 (0.11)	0.66 (0.08)	0.66
BP-systolic (182)	114.4 (16.2)	112.2 (12.2)	115.9 (18.3)	113.4 (14.8)	0.41
BP-diastolic (182)	66.2 (9.1)	64.9 (9.3)	67.2 (9.3)	65.5 (8.3)	0.31
Total Body fat % (146)	42.2 (8.7)	44.4 (8.0)	41.3 (8.5)	42.1 (9.5)	0.22
Truncal fat % (146)	36.7 (9.6)	39.0 (8.8)	35.7 (8.1)	35.8 (11.1)	0.25
Biochemistry					
GGT* (189)	22.3 (14.0)	24.4 (11.6)	21.0 (12.3)	22.9 (18.1)	0.39
ALT* (188)	37.3 (26.6)	42.4 (23.1)	36.7 (31.4)	33.9 (18.7)	0.29
Fasting glucose† (193)	4.59 (0.50)	4.70 (0.67)	4.53 (0.41)	4.61 (0.47)	0.17
Fasting insulin† (186)	23.2 (16.9)	27.1 (18.4)	21.2 (14.6)	23.7 (19.2)	0.16
2 hour glucose† (84)	6.33 (1.53)	6.46 (1.00)	6.14 (1.53)	6.68 (1.96)	0.41
HbA1c (135)	5.41 (0.60)	5.34 (0.39)	5.38 (0.76)	5.51 (0.38)	0.44
Cholesterol† (192)	4.53 (0.73)	4.71 (0.68)	4.48 (0.77)	4.48 (0.68)	0.18
Triglycerides† (188)	1.23 (0.61)	1.25 (0.55)	1.18 (0.55)	1.30 (0.76)	0.50
HDL-C† (115)	1.25 (0.28)	1.32 (0.31)	1.23 (0.27)	1.22 (0.26)	0.31
LDL-C† (115)	2.72 (0.66)	2.85 (0.65)	2.69 (0.75)	2.68 (0.49)	0.53

years *IU/L †mmol/L *WHtR* waist-height ratio

Results (cont.)

Table 2. Definitions of obesity-related comorbidities in obese children and adolescents. (references available upon request)

Comorbidity	Definition
1. Prediabetes	Either: impaired fasting glucose (IGT) ≥5.6 mmol/L (n=10), impaired glucose tolerance 2 hour glucose ≥7.8 mmol/L on OGTT testing or HbA1c ≥5.7%.
Type 2 Diabetes Mellitus	Either: elevated fasting glucose ≥7.0 mmol/L, elevated 2 hour glucose ≥11.1 mmol/L on OGTT testing or HbA1c ≥6.5% AND the absence of diabetic autoantibodies
2. Hypertension	Systolic and/or blood pressure ≥ 90th percentile for age and sex
3. Hyperlipidaemia	Presence of one of more of the following: Total cholesterol ≥ 5.2 mmol/L; Triglycerides ≥ 1.13 mmol/L (age 0-9 years) or ≥1.5 mmol/L (age 10-19 years); LDL-C ≥ 3.4 mmol/L; HDL-C ≤ 1.04 mmol/L
4. Non-alcoholic fatty liver disease	Elevated ALT or GGT as defined by the age-specific laboratory reference intervals AND/OR the presence of fatty infiltrates on liver ultrasonography, in the absence of other liver pathology.
5. Obstructive sleep apnoea	Clinical suspicion of OSA if one or more of the following is present on history: Snoring, laboured, paradoxical or obstructed breathing, sleepiness, hyperactivity, behavioural problems or learning problems. AND/OR the presence of one or more of the following on polysomnogram, if performed: One or more obstructive apneas, mixed apneas, or hypopneas per hour of sleep. A pattern of obstructive hypoventilation with snoring, flattening of nasal pressure waveform or paradoxical thoracoabdominal motion.
6. Mental health	Pre-existing diagnosis of depression, anxiety disorder and/or history of self harm/suicidal ideations
7. Orthopaedic	The presence of slipped capital femoral epiphysis and/or Blount disease.
8. Eating disorder	Pre-existing diagnosis or clinical suspicion of one or more of the following: Body image disturbance, eating disorder, including anorexia, bulimia.
9. Neurological	The presence of one or more of the following in the absence of other neurological diagnosis: Headache with nausea, vomiting, retroocular eye pain, transient visual obscurations, visual loss, or diplopia; Papilloedema or radiological signs of raised intracranial pressure.

Dietary survey analysis revealed minor differences between FTO genotype groups in vitamin A and retinol intake (additive/ recessive modelling) as well as protein, polyunsaturated fat and cholesterol intake (recessive modelling). (**Table 3**)

Table 3. Comorbidities, food intake and exercise levels in a group of obese youth attending WMS, participants grouped by FTO rs9939609 SNP genotype. (A allele is the risk allele)

	All†	AA (n=45)	AT (n=100)	TT (n=52)	p‡	p§	p#
A. Comorbidities							
Comorbidity score	1.70 (1.3)	1.87 (1.3)	1.6 (1.2)	1.7 (1.4)	0.50	0.82	0.31
B. Activity (n=80)							
Sedentary*	624 (100)	616 (112)	523 (93)	641 (107)	0.76	0.66	0.48
MVPA*	41.5 (22.9)	46.2 (24.8)	40.1 (24.0)	38.6 (15.9)	0.54	0.27	0.61
C. Dietary Intake (n=83)							
Total intake – Macronutrients							
Energy (kJ)	8901 (3035)	9744 (3275)	8709 (2768)	8461 (3386)	0.35	0.16	0.49
Protein (g)	90.5 (30.4)	102.4 (31.9)	86.0 (27.3)	88.8 (34.3)	0.13	**0.045**	0.79
Fats (g)	72.5 (27.7)	82.4 (28.8)	70.4 (26.1)	66.8 (29.0)	0.16	0.07	0.32
Satfats¶ (g)	33.0 (14.1)	37.5 (14.6)	32.9 (14.2)	28.6 (12.2)	0.15	0.11	0.13
Polyfats^ (g)	7.8 (3.1)	9.11 (3.60)	7.25 (2.41)	7.74 (3.70)	0.08	**0.029**	0.92
Monofats (g)	25.3 (9.6)	28.7 (10.0)	24.2 (8.6)	24.3 (11.0)	0.20	0.07	0.63
Cholesterol (g)	279 (115)	331 (134)	256 (91)	280 (134)	0.05	**0.02**	0.98
Carbohydrate (g)	267 (99)	272 (106)	266 (92)	255 (109)	0.71	0.46	0.56
Sugars (g)	142 (62)	142 (68)	146 (63)	129 (54)	0.61	0.97	0.33
Water (g)	2796 (941)	2760 (1117)	2823 (849)	2766 (1003)	0.96	0.85	0.88
Fibre (g)	26.7 (11.7)	29.8 (12.0)	25.5 (10.3)	26.3 (14.6)	0.39	0.17	0.87
Total intake - micronutrients							
Thiamine (mg)	1.63 (0.73)	1.84 (0.76)	1.54 (0.56)	1.6 (1.03)	0.31	0.14	0.98
Riboflavin (mg)	2.34 (1.1)	2.73 (0.99)	2.27 (1.11)	2.09 (1.13)	0.16	0.07	0.27
Niacin (mg)	20.7 (7.7)	23.6 (8.5)	19.3 (6.3)	21.0 (9.4)	0.11	0.054	0.84
Vitamin C (mg)	165.3 (88.4)	170.2 (87.0)	165.1 (92.9)	160.4 (82.7)	0.95	0.78	0.79
Folate (µg)	315 (132)	363 (139)	301 (119)	296 (147)	0.17	0.058	0.49
Vitamin A (mg)	1315 (778)	1737 (1163)	1240 (556)	1031 (547)	**0.01**	**0.005**	0.08

* minutes † M (SD) or N (%) ‡ additive model § recessive model
# dominant model
^polyunsaturated fat ¶saturated fat

FTO AA genotype participants were twice as likely to have OSA than those with AT or TT genotypes (unadjusted OR 2.54 [CI: 1.20-5.4], *p=0.015,* **Table 4**). This effect remained significant after adjusting for either total percentage body fat, sex, age and pubertal status or BMI z-score.

Table 4. Obesity-related comorbidities in obese youth by FTO rs9939609 SNP genotype.

	Recessive model					
Comorbidity (n)	OR [CI]	p	Adjusted OR* [CI]	p	Adjusted OR# [CI]	p
HTN (182)	0.77 [0.38-1.54]	0.46	0.47 [0.20-1.11]	0.087	0.76 [0.39-1.54]	0.46
Pre-diabetes (117)	0.95 [0.38-2.33[	0.91	1.11 [0.39-3.19]	0.84	0.95 [0.39-2.35]	0.92
IR† (188)	1.78 [0.89-3.58]	0.10	1.26 [0.53-3.00]	0.60	1.77 [0.88-3.55]	0.11
Lipid‡ (197)	1.84 [0.90-3.78]	0.10	1.98 [0.85-4.63]	0.11	1.91 [0.92-3.94]	0.08
NAFLD (196)	0.94 [0.46-1.93]	0.87	0.87 [0.36-2.14]	0.77	0.93 [0.45-1.92]	0.85
OSA (197)	2.54 [1.20-5.4]	**0.015**	3.25 [1.27-8.33]	**0.014**	2.55 [1.19-5.45]	**0.015**
MH (197)	1.08 [0.40-2.88]	0.88	0.84 [0.27-2.67]	0.77	1.07 [0.40-2.88]	0.89
Ortho (197)	2.31 [0.37-14.3]	0.37	0.98 [0.09-10.6]	0.99	2.31 [0.37-14.3]	0.37
T2DM (192)	2.37 [0.38-14.7]	0.35	2.01 [0.31-13.3]	0.47	2.37 [0.38-14.7]	0.35

* adjusted for total percentage body fat, sex, age and pubertal status
# adjusted for BMI z-score † Insulin resistance ‡ Hyperlipidaemia
HTN hypertension *MH* mental health disorder *Ortho* Orthopaedic disorders

Take Home Points

Negative Finding: Risk allele was not associated with adiposity.
Within our cohort of overweight and obese youth, no association was seen between the FTO risk allele and adiposity, although the minor allele frequency of the FTO rs9939906 SNP was similar to previous reports (2). The FTO risk allele was not associated with changes in energy intake or physical activity levels in our cohort. Neither was it associated with impaired glucose metabolism, as found in previous studies (3, 4).

Supporting Finding: Dietary differences between FTO genotype groups.
As shown in previous reports (5, 6), the FTO risk allele was associated with higher protein, polyunsaturated fat, cholesterol, vitamin A and retinol intake in our cohort.

Novel Finding: FTO associated with OSA independent of BMI-Z
Our study found an association between homozygous FTO risk genotype and clinical suspicion of OSA at baseline assessment of obese youth, which is independent of total adiposity and BMI-Z.

Conclusion

Recessive FTO risk allele genotype was associated with increased presentation of clinical paediatric OSA, independent of body fat percentage. FTO genotype may independently or synergistically magnify the burden of obesity-related comorbidities.

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