Allelic variation in key performance genes are linked with increased severity of obesity in overweight/obese youth

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Introduction

Childhood obesity is common and is associated with type 2 diabetes mellitus and heart disease [1]. Obesity mainly arises from an imbalance between energy intake and expenditure, although some children appear to carry a genetic predisposition for weight gain. The ability to sustain physical activity and its potential for health benefits is genetically predetermined. Candidate genes for performance and muscle strength have been shown to substantially influence muscle function and mass in response to exercise [2]. Whether variations in genetic performance traits affect a child's propensity to weight gain, in the setting of obesity, has not been investigated.

Aim

To determine whether there is a genetic predisposition in some obese children that limits their muscle's ability to train and utilise substrates effectively, thereby perhaps associate with worsening of adiposity measures, elevated blood pressure and reduced physical activity.

Methods

Investigations were performed in the Childhood Overweight BioRepository of Australia (COBRA) study, Australia`s largest longitudinal overweight and obese paediatric cohort (RCH Ethics 28081)[3]. DNA for genotyping was extracted from peripheral blood mononuclear cells (N=234; Mean BMI z-score 2.45, SD 0.44). SNP analysis was undertaken on a unique fitness gene panel using iPlex chemistry on the Sequenom MassARRAY.
Logistic regression analysis between allele prevalence and outcomes (BMI z-scores, body fat percentage, waist circumference, blood pressure and accelerometer data) was performed, adjusted for sex, age and BMI z-score where applicable. Significance was taken as $p<0.05$.

Results

Participant characteristics

Variable	N	Mean ±SD	%
Age (years)	234	11.3 ±3.6	
Females	234		53
BMI (kg/m2)	234	32.6 ±7.4	
BMI z-score	234	2.45 ±0.44	
Waist circumference (cm)	192	101 ±21	
Body fat (%)	191	42.1 ±8.4	
Systolic BP (mmHg)	218	113 ±16	
Diastolic BP (mmHg)	218	66 ±9	
Accelerometer activity	78	238 ±95	

- Overall lower allele prevalence for performance genes in obese children compared to reference populations.
- Allele prevalence for performance genes was associated with adiposity measures such as BMI, waist circumference in females but not male participants.
- Sex dependent variation was also observed between allele prevalence and blood pressure.
- Physical activity was associated for 5 key genes.

Significant associations between performance genes and outcome measures

Gene (Genotype 1/2/3)	Genotype1	Genotype2	Genotype3	p-value
BMI				
♀ ACTN3 (**T**T/CT/CC)	2.45±0.40	2.51±0.45	2.66±0.47	0.047
♀ ZFYVE26 (**A**A/AG/GG)	2.57±0.58	2.66±0.47	2.43±0.38	0.04
♀ CNDP1 (**A**A/GA/GG)	2.79±0.61	2.57±0.36	2.42±0.44	0.0003
Waist circumfrence				
♀ RPLP1_GEMIN8P1 (**T**T/CT/CC)	87±19	100±20	105±21	0.008
Body Fat %				
♀ IL15RA (**T**T/GT/GG)	46.1±8.3	42.1±7.4	40.8±7.0	0.03
♂ SHBG_GENE (**T**T/GT/GG)	26.8±3.2	40.2±8.6	43.5±9.1	0.008
Systolic BP				
♀ UGT2B4 (**G**G/GT/TT)	113±18	117±18	109±12	0.046
♂ GALNT13 (**G**G/AG/AA)	130±11	116±15	112±17	0.006
♂ PPARGC1A (**T**T/CT/CC)	121±19	116±16	110±14	0.02
Diastolic BP				
♂ GALNT13 (**G**G/AG/AA)	71±7	68±9	65±9	0.03
Accelerometer activity				
♀ CNDP1 (**A**A/GA/GG)	161±44	219±89	275±100	0.003
♀ HIF1A (**T**T/CT/CC)	n/a	301±108	216±86	0.02
♀ CRHBP (**T**T/CT/CC)	266±107	188±62	221±71	0.03
♀ ZFYVE26 (**A**A/AG/GG)	282±105	266±109	192±64	0.002
♂ SHBG_GENE (**T**T/GT/GG)	255±n/a	212±75	239±104	0.04

*Results after logistic regression between effect allele **(in bold)** prevalence and outcomes (BMI, waist, body fat, systolic BP, diastolic BP and step count). Analysis are adjusted for sex and age. Results for systolic and diastolic BP are adjusted for BMI z-scores.*

Comparison of genotype prevalence with COBRA participants

Gene	Effect Allele	SNP	1000 genomes	Highest population	COBRA Allele Frequency
ACTN3	T	rs1815739	0.4	0.49	0.32
GALNT13	G	rs10196189	0.22	0.48	0.12
HIF1A	T	rs11549465	0.07	0.19	0.06
GALNTL6	A	rs558129	0.23	0.38	0.2
IL15RA	T	rs2228059	0.45	0.5	0.37
SHBG	T	rs12150660	0.09	0.28	0.14
ZFYVE26	A	rs12891164	0.23	0.43	0.19
CREM	T	rs1531550	0.17	0.29	0.11
BMP2	C	rs15705	0.28	0.49	0.16
CRHBP	T	rs1715747	0.49	0.49	0.51
UGT2B4	G	rs17671289	0.17	0.35	0.15
LOC105375384	A	rs17766292	0.44	0.49	0.48
NEUROD1	T	rs1801262	0.23	0.43	0.24
TNFRSF11A	C	rs1805034	0.41	0.49	0.35
NFATC4	C	rs2229309	0.28	0.49	0.42
SPP1	G	rs28357094	0.1	0.27	0.15
GPX5	T	rs28382609	0.05	0.14	0.02
CNDP1	A	rs2887	0.37	0.48	0.24
PPARA	C	rs4253778	0.27	0.41	0.12
RPLP1-GEMIN8P1	T	rs4776471	0.33	0.44	0.32
AKAP13	G	rs4843075	0.42	0.5	0.2
DLC1	T	rs532841	0.5	0.5	0.38
UBE3B	G	rs7298565	0.48	0.5	0.35
CNDP2	A	rs734559	0.22	0.49	0.13
PLCG1	T	rs753381	0.27	0.48	0.31
PPARGC1A	T	rs8192678	0.27	0.5	0.23
DMD	A	rs939787	0.26	0.38	0.13

Take Home Points

1. **Severely obese children are less likely to exhibit a 'performance genotype'** which may confer a greater risk for further weight gain and cardio-metabolic complications.
2. Small nuclear polymorphisms associated with adiposity measures (BMI, waist circumference and body fat) were mainly found in females
3. SNP's in performance genes were associated with systolic and diastolic blood pressure alterations in both sexes
4. Overall, allele prevalence and documented effects on performance only partially correlated with adiposity measures, BP and activity

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