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Background

- Dysregulation of energy homeostasis leads to overweight and obesity.
- The hypothalamic nutrient sensing networks such as the *mTOR* pathway, integrate hormonal and nutritional signals to regulate energy homeostasis.
- Although genome-wide association studies have revealed 396 obesity-related loci to date, data in Asian type 2 diabetes (T2D) populations remain sparse.

Aim

To examine the association between *mTOR* genetic variants and anthropometric traits in Chinese with T2D.

Methods

- Cross-sectional analysis of a consecutive cohort of 6445 patients with T2D from the Hong Kong Diabetes Registry recruited between 1994 and 2007.
- Fasting blood samples were genotyped for 35 single nucleotide polymorphisms (SNPs) with minor allele frequency $\geq 1\%$ within *mTOR* genetic locus using Illumina Omni 2.5+ exome array.
- After filtering SNPs with high linkage disequilibrium using $r^2 > 0.8$, we examined the associations between 14 SNPs and baseline anthropometric traits in an additive model.
- Linear and logistic regression analyses were stratified by sex, adjusting for age, duration of diabetes, principal components of global ancestry and BMI, as appropriate.

TABLE 1: Definitions of overall and central adiposity

Anthropometric traits	Sample size (Men vs. Women)	Definitions
Body mass index (BMI, kg/m ²)	5892 (2724 vs. 3168)	Underweight : <18.5 Normal weight : 18.5 - <23.0 Overweight : 23.0 - <25.0 Obesity : 25.0 - <30.0 Severe obesity : ≥ 30.0
Waist circumference (WC, cm)	5719 (2604 vs. 3115)	Men: ≥ 90 Women: ≥ 80
Waist-hip ratio (WHR)	5436 (2488 vs. 2948)	Men: ≥ 0.90 Women: ≥ 0.85

Results

- Nearly 70% of the study cohort had overweight and obesity.
- Using WC and WHR cut-offs, increased central adiposity was reported in 1057 (40.6%) and 1518 (61.0%) men, respectively. The corresponding figures in women were 1895 (60.8%) and 1708 (57.9%).
- rs12122605** showed **significant sex interaction for WC adjusted for BMI** (beta_{men} -0.263, beta_{women} 0.160, $P_{\text{sex-interaction}}$ 0.048).

- rs11121691** showed **significant sex-interaction for WHR adjusted for BMI** (beta_{men} 0.005, beta_{women} -0.004, $P_{\text{sex-interaction}}$ 0.046).

TABLE 2: Baseline characteristics of the study cohort

Variables	Total (N=6445)	Men (N=3011)	Women (N=3434)	P-value
Age (years)	57.6 (12.9)	57.6 (12.5)	57.6 (13.3)	0.933
Disease duration [†] (years)	6 (2-12)	5 (1-10)	6 (2-12)	<0.001
BMI	25.2 (4.0)	25.2 (3.9)	25.2 (4.1)	0.953
WC	85.8 (10.1)	88.6 (9.8)	83.5 (9.9)	<0.001
WHR	0.89 (0.07)	0.92 (0.06)	0.87 (0.06)	<0.001
HbA _{1c}	7.6 (1.8)	7.7 (1.8)	7.6 (1.7)	0.025
Systolic BP	135.6 (20.8)	134.4 (19.5)	136.7 (21.7)	<0.001
LDL-cholesterol	3.1 (1.0)	3.0 (1.0)	3.2 (1.0)	<0.001
HDL-cholesterol	1.3 (0.4)	1.2 (0.3)	1.4 (0.4)	<0.001
Triglyceride [†]	1.4 (1.0-2.1)	1.4 (1.0-2.1)	1.4 (1.0-2.1)	0.138
Metabolic syndrome	3976 (68.8%)	1629 (61.8%)	2348 (74.7%)	<0.001

Data are expressed as mean (standard deviation), median (interquartile range)[†] or number (percentages). Metabolic parameters are in SI units. BP, blood pressure.

TABLE 3: Association of 14 genotyped SNPs with overall adiposity

dbSNP ID	BMI ≥ 30 vs. <30 (N=584 vs. 5125)		BMI ≥ 30 vs. normal weight (N=584 vs. 1564)	
	OR (95% CI)	P-value	OR (95% CI)	P-value
rs12133922	1.06 (0.89-1.25)	0.523	1.07 (0.88-1.29)	0.511
rs11121691	1.06 (0.81-1.39)	0.679	0.94 (0.68-1.28)	0.675
rs58268656	1.37 (0.98-1.90)	0.064	1.26 (0.87-1.83)	0.229
rs17848553	1.37 (0.98-1.90)	0.064	1.26 (0.87-1.83)	0.229
rs77086655	1.34 (0.97-1.86)	0.077	1.24 (0.86-1.80)	0.256
rs6701524	1.06 (0.83-1.35)	0.642	0.95 (0.71-1.26)	0.699
rs2791643	0.94 (0.72-1.24)	0.673	1.07 (0.78-1.47)	0.675
rs12122605	1.17 (1.00-1.36)	0.046	1.18 (0.99-1.40)	0.062
rs28990992	1.36 (0.98-1.89)	0.067	1.26 (0.87-1.83)	0.229
rs2076658	1.08 (0.87-1.34)	0.506	1.06 (0.83-1.36)	0.628
rs1135172	0.87 (0.71-1.07)	0.178	0.97 (0.77-1.22)	0.780
rs72633721	0.84 (0.53-1.35)	0.475	0.79 (0.46-1.37)	0.404
rs4845988	0.89 (0.76-1.03)	0.112	0.95 (0.80-1.13)	0.593
rs6685950	1.31 (1.07-1.60)	0.009	1.28 (1.02-1.61)	0.035

Discussion

Significant nominal associations between three *mTOR* genetic variants with overall and central adiposity were identified in Chinese with T2D. Sexual dimorphism was evident in waist-related traits.