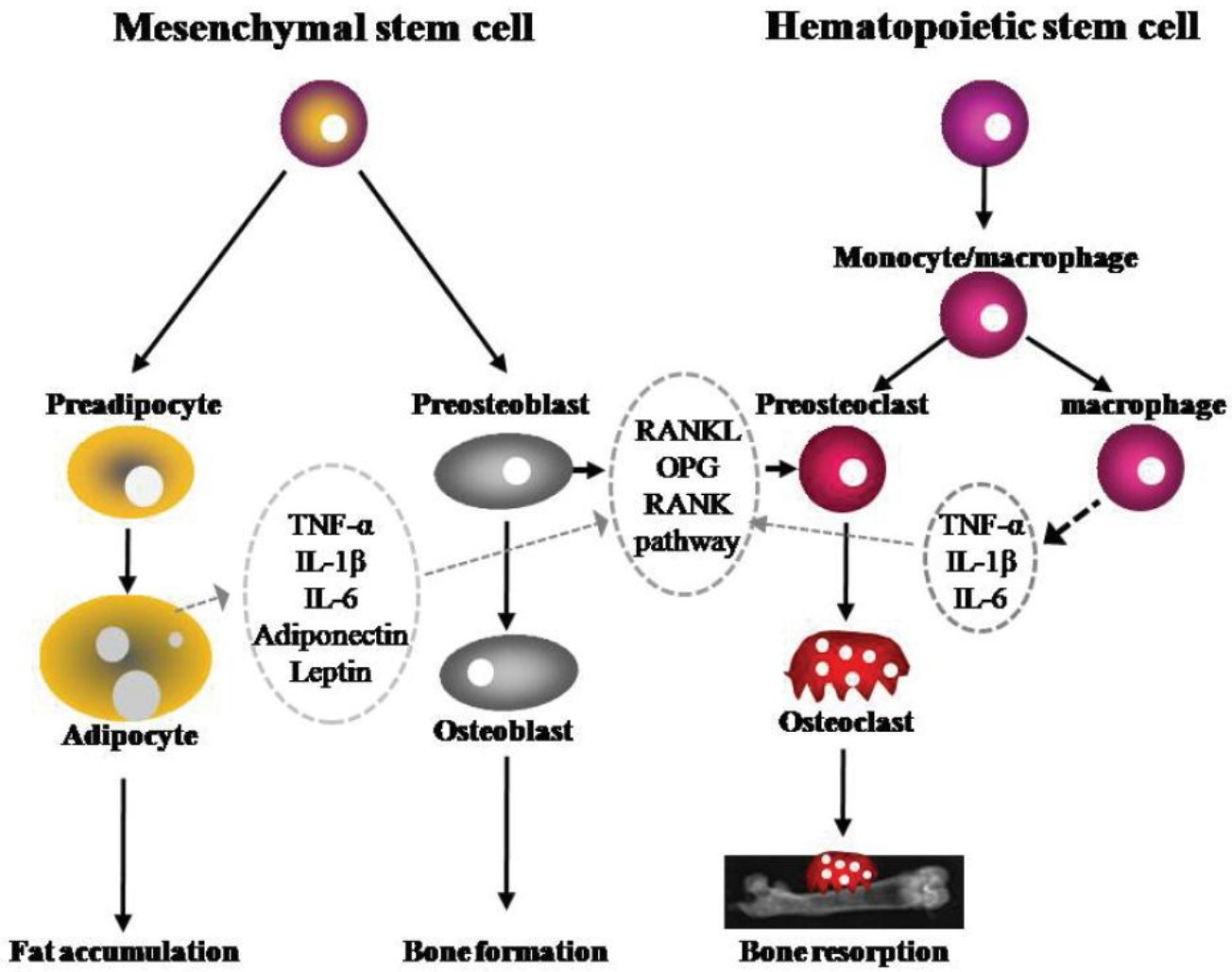
FTO gene and bone mineral density

Presented by Asst. Prof. Daruneewan Warodomwichit

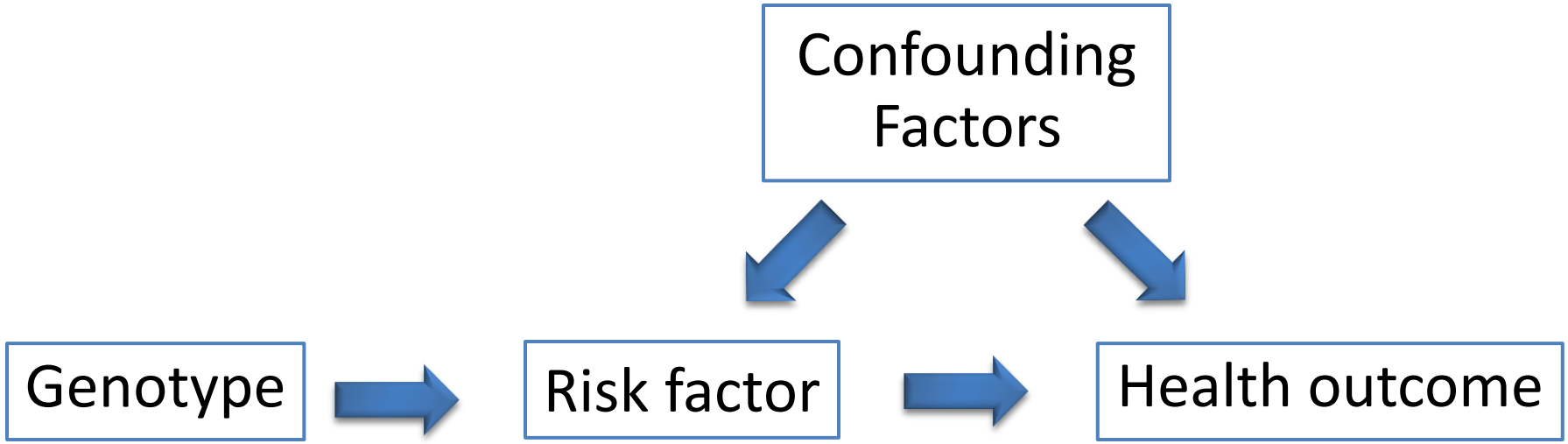
Obesity and Osteoporosis

- A number of risk factors are related to susceptibility to osteoporosis, including estrogen deficiency, sedentary lifestyle and reduced adiposity.
- Adipose tissue is now considered an endocrine organ. It secretes a number of bioactive proteins which influence a variety of biological processes, including energy homeostasis and inflammation.
- As far as bone is concerned, leptin, an adipokine secreted from adipose tissue, has been shown to diminish bone formation through a central nervous system delay in animal models. In humans, a number of adipokines, including leptin, adiponectin and omentin-1, have been shown in observational studies to be variably related to bone mineral density (BMD).
- Results from observational studies can be confounded by factors which influence both adiposity and bone mass, such as body size and weight. Moreover, the causality of adipose tissue on bone mass and the direction of net influence have not been directly assessed in adult humans.

Bone metabolism regulated by adipocytes, osteoblasts, and osteoclasts



Mendelian Randomisation framework



Key assumptions of the Mendelian Randomozation

- The genetic variant is unrelated to (independent of) the typical confounding factors.
- The genetic variant is (reliably) associated with the exposure and we can accurately quantify the relationship this represents.
- There is no direct effect of genotype on disease nor any other mediated effect other than through the exposure of interest.
- If the three key assumptions of an instrumental variable are satisfied by the genetic variant, testing for a causal effect of phenotype on disease by testing for an association between genotype and disease is straightforward for most practical purposes.

Variation in *FTO* contributes to childhood obesity and severe adult obesity

nature genetics

2900 affected individuals and 5100 control

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Sciencexpress Report

A Common Variant in the *FTO* Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity

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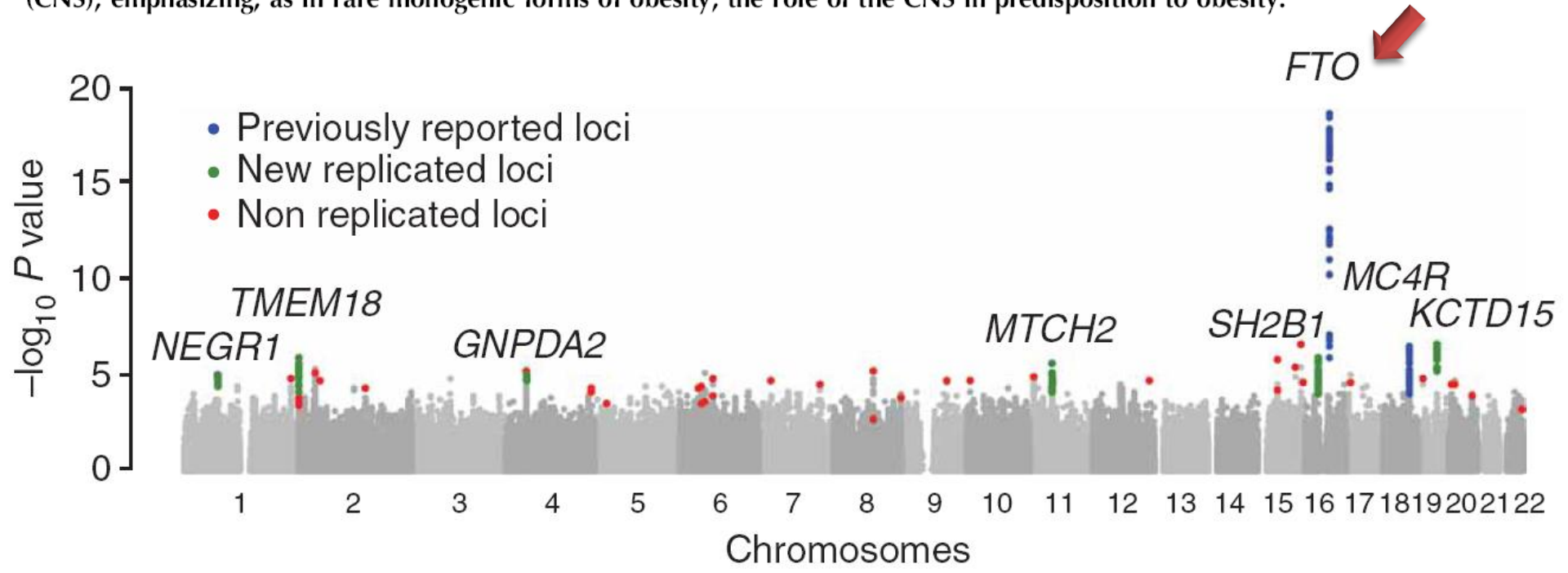
13 cohorts with 38,759 participants
homozygous for the risk allele weighed about 3 kilograms more and had a 1.67-fold increased risk of obesity

Received 7 July; accepted 15 October; published online 14 December 2008; doi:10.1038/ng.287

nature genetics

Six new loci associated with body mass index highlight a neuronal influence on body weight regulation

Common variants at only two loci, *FTO* and *MC4R*, have been reproducibly associated with body mass index (BMI) in humans. To identify additional loci, we conducted meta-analysis of 15 genome-wide association studies for BMI ($n > 32{,}000$) and followed up top signals in 14 additional cohorts ($n > 59{,}000$). We strongly confirm *FTO* and *MC4R* and identify six additional loci ($P < 5 \times 10^{-8}$): *TMEM18*, *KCTD15*, *GNPDA2*, *SH2B1*, *MTCH2* and *NEGR1* (where a 45-kb deletion polymorphism is a candidate causal variant). Several of the likely causal genes are highly expressed or known to act in the central nervous system (CNS), emphasizing, as in rare monogenic forms of obesity, the role of the CNS in predisposition to obesity.

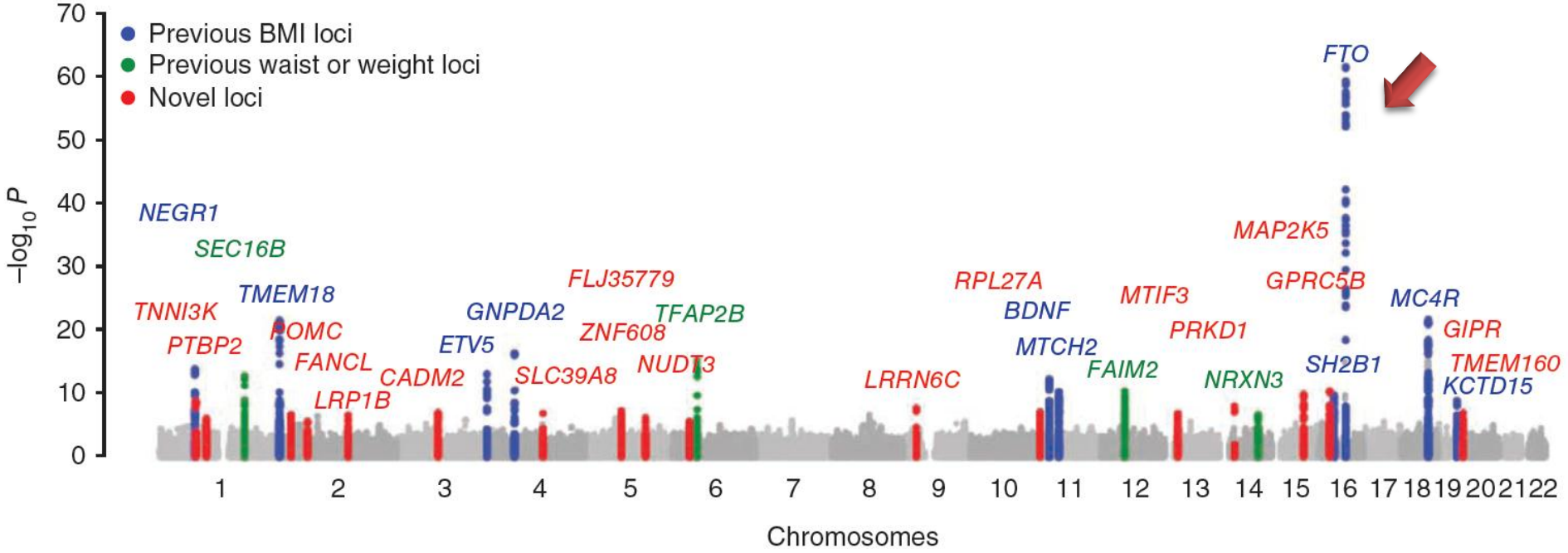


Received 13 May; accepted 15 September; published online 10 October 2010; doi:10.1038/ng.686

nature genetics

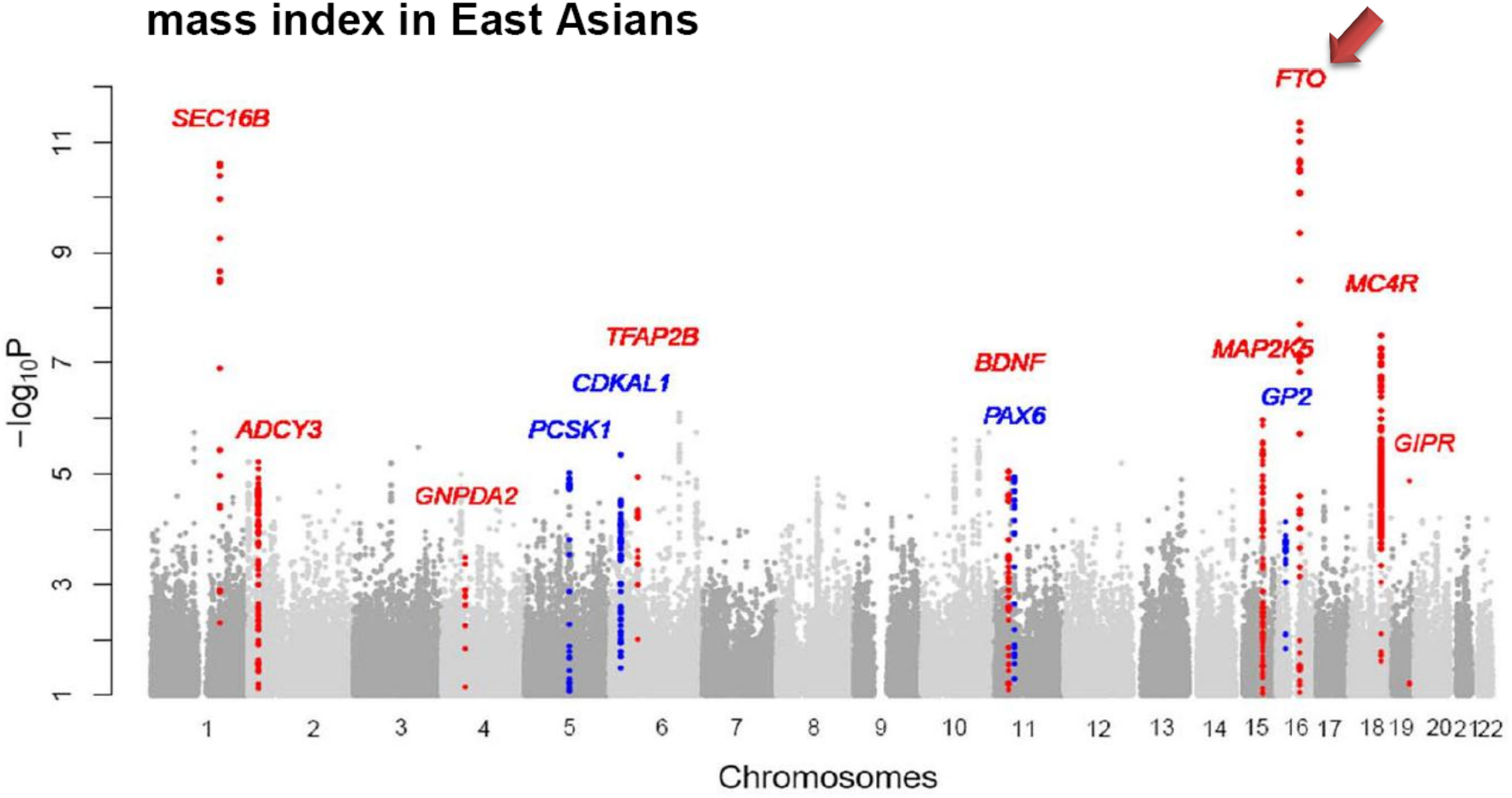
Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index

Obesity is globally prevalent and highly heritable, but its underlying genetic factors remain largely elusive. To identify genetic loci for obesity susceptibility, we examined associations between body mass index and ~2.8 million SNPs in up to 123,865 individuals with targeted follow up of 42 SNPs in up to 125,931 additional individuals. We confirmed 14 known obesity susceptibility loci and identified 18 new loci associated with body mass index ($P < 5 \times 10^{-8}$), one of which includes a copy number variant near *GPRC5B*. Some loci (at *MC4R*, *POMC*, *SH2B1* and *BDNF*) map near key hypothalamic regulators of energy balance, and one of these loci is near *GIPR*, an incretin receptor. Furthermore, genes in other newly associated loci may provide new insights into human body weight regulation.

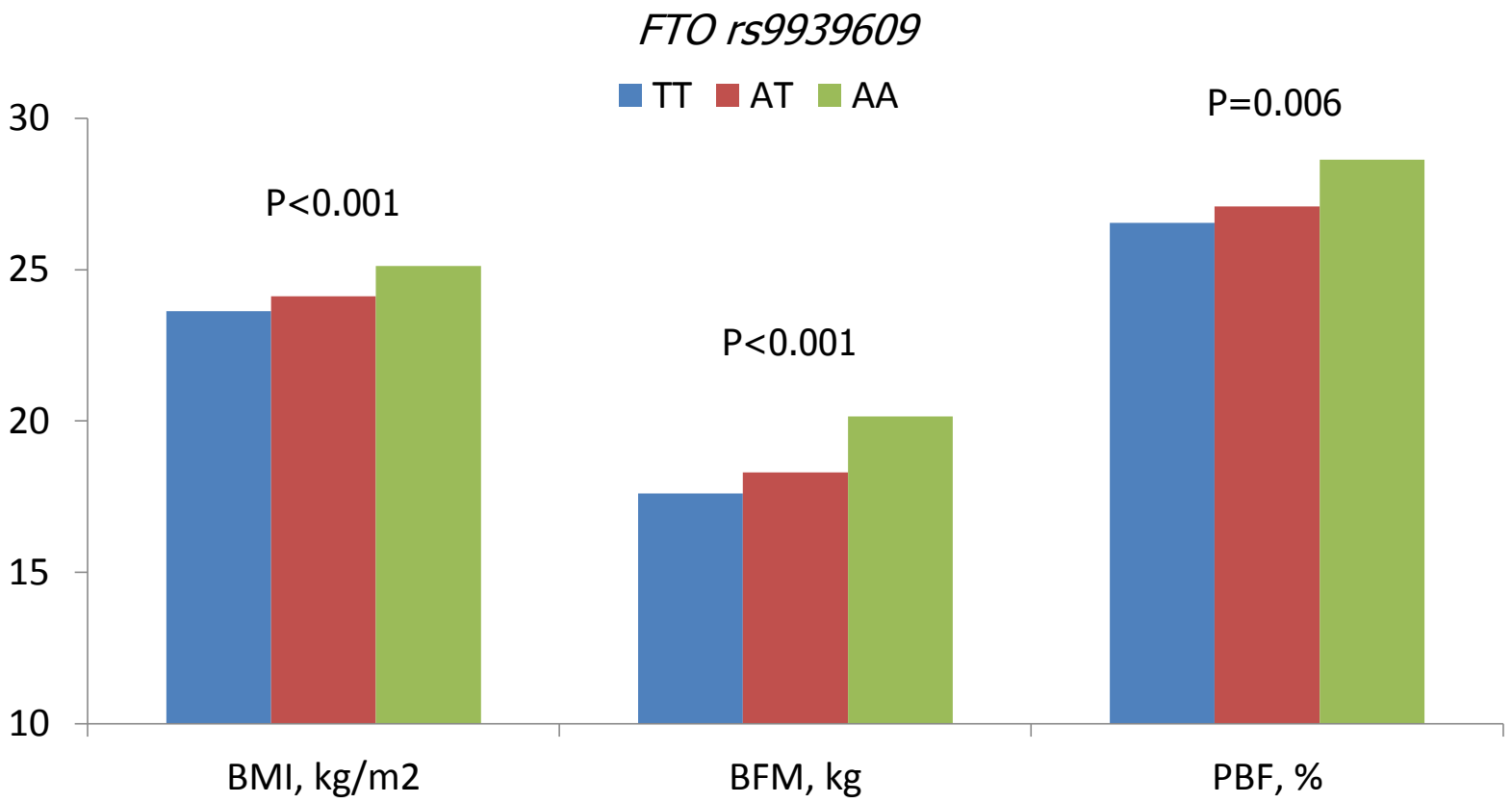


Published in final edited form as:
Nat Genet. ; 44(3): 307–311. doi:10.1038/ng.1087.

Meta-analysis identifies common variants associated with body mass index in East Asians

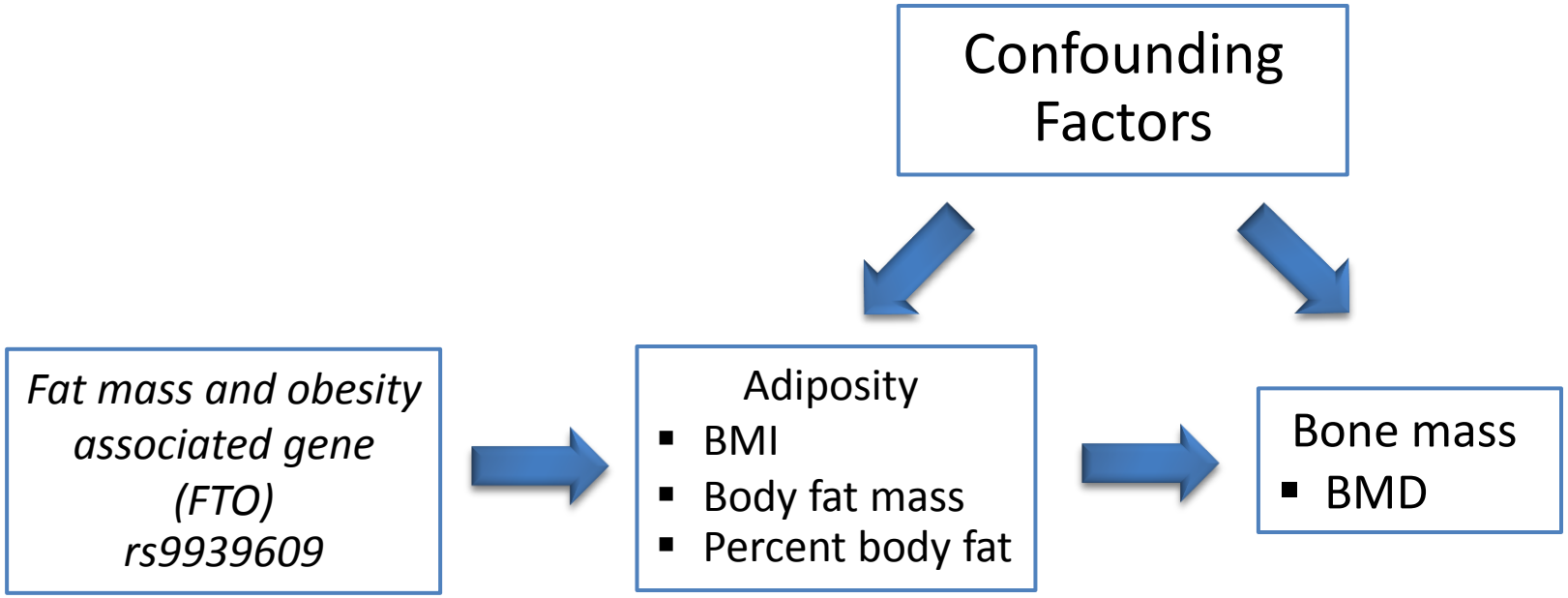


Association of FTO and adiposity

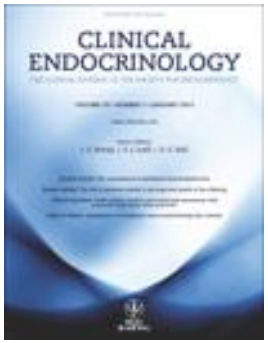


Applying linear regression analysis by fitting *FTO* as an additive effect suggests that the *FTO* polymorphism was significantly correlated with BMI (coefficient = 0.637 kg/m^2, p < 0.001); indicating that carrying an A allele would increase BMI of 0.637 kg/m^2.

Causal inference of the effect of adiposity on Bone mass



Candidate gene for obesity
Located on chromosome 16q12.2



Received Date : 4-May-2012
Returned for Revision: 1-Jun-2012
Finally Revised Date : 21-Sep-2012
Accepted Date : 21-Sep-2012
Article category : B

Causal inference of the effect of adiposity on bone mineral density in adults

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Running title: Causal effect of adiposity on bone mineral density

Materials and methods

- The participants in the EGAT 3/1 who have complete data of body composition, genotype, and BMD (n=2154).
- Body composition was evaluated using multi-frequency bioelectrical impedance analysis with eight-point tactile electrodes (InBody 720; Biospace, Seoul, Korea).
- Genotyping of *FTO rs9939609 SNP (*TaqMan® MGB probes) was performed using real-time PCR system (Applied Biosystems, Foster City, CA).
- Bone mineral density was assessed using dual-emission X-ray absorptiometry (DXA) (Hologic QDR 4500W; Bedford, MA) at the lumbar spine (L1–L4) and left proximal femur (femoral neck and total hip)

Statistical analysis

- Hardy–Weinberg equilibrium was assessed using an exact test.
- Relationships between the *FTO polymorphism and variables were* assessed using linear regression and a chi-square test for continuous and categorical data, respectively.
- Mendelian randomization analysis was applied to assess causal relationships between *FTO, adiposity and BMD.*
- *Instrumental variable (IV)* regression with two-stage least squares method was applied to explore these causal relationships, using the *FTO polymorphism with additive effect as the IV and BMI/body* fat mass as the endogenous variables
- These models were also adjusted for confounding variables (i.e. alcohol, age and gender), since univariate analysis suggested that they were associated with intermediate phenotype and/or BMD
- In the first-stage regression, the F–statistic (hereafter called F-First) was used to assess whether the *FTO* polymorphism was sufficiently strong to be an IV. A value of F-First greater than 10 indicated that the *FTO was a strong IV, and thus the estimated causal relationships should* be valid.
- In addition, linear regression with ordinary least squares (OLS) method was also applied to directly assess the association between *FTO, adiposity and BMD. The Durbin*– Wu–Hausman statistic was applied to compare the results between the IV and OLS regression approaches.
- All analyses were performed using STATA version 12.0. A *P value* of less than 0.05 was considered statistically significant.

Clinical characteristics of cohort

Characteristic	Mean (SD)
Age (years)	40.0 (7.4)
Body weight (kg)	66.1 (12.5)
Height (cm)	166.2 (7.8)
BMI (kg/m^2)	23.9 (3.6)
Body fat mass (kg)	17.9 (6.6)
Percent body fat (%)	26.8 (7.2)
Cigarettes smoking/day, median (range)	0 (0–50)
Alcohol consumption, number (%)	982/2,325 (42.2)
Lumbar spine BMD (g/cm^2)	0.975 (0.118)
Femoral neck BMD (g/cm^2)	0.801 (0.121)
Total femur BMD (g/cm^2)	0.925 (0.129)

Correlation matrix between measures of adiposity and BMD

	BMI	Body fat mass(kg)	Body fat mass(%)	Lumbar BMD	Femoral neck BMD	Total femur BMD
BMI	1.0000					
Body fat mass(kg)	0.85 (< 0.001)	1.0000				
Body fat mass(%)	0.51 (<0.001)	0.82 (<0.001)				
Lumbar BMD	0.19 (< 0.001)	0.14 (< 0.001)	0.03 (0.13)	1.0000		
Femoral neck BMD	0.39 (< 0.001)	0.23 (< 0.001)	-0.02 (0.39)	0.62 (< 0.001)	1.0000	
Total femur BMD	0.39 (< 0.001)	0.22 (< 0.001)	-0.03 (0.162)	0.57 (< 0.001)	0.81 (< 0.001)	1.0000

Association between FTO and Potential confounders of adiposity and BMD

Characteristic	*FTO* genotype			*P*-value
	TT (n = 1315)	AT (n = 731)	AA (n = 108)	
Age, mean (SD)	40.1 (6.9)	40.0 (6.9)	40.3 (6.8)	0.500
Gender				
Male	949 (72.2%)	532 (72.8%)	79 (73.2%)	0.955
Female	366 (27.8%)	199 (27.2%)	29 (26.8%)	
Alcohol consumption				
Yes	565 (43.0%)	305 (41.7%)	46 (42.6%)	0.941
No	749 (57.0%)	426 (58.3%)	62 (57.4%)	
Cigarette smoking, median (range)	0 (0,50)	0 (0,30)	0 (0,15)	0.526

Linear and IV regression analysis of the relationships between BMD and BMI

BMI (kg/m²)	Linear regression			IV regression				
	β	95% CI	P-value	β	95% CI	P-value	F-First*	WH P-value**
Total hip BMD (g/cm²)	0.0138	0.0124, 0.0153	< 0.001	0.0189	0.0046, 0.0332	0.010	25.734	0.486
Femoral neck BMD (g/cm²)	0.0119	0.0107, 0.0132	< 0.001	0.0149	0.0030, 0.0268	0.014	21.864	0.629
Total spine BMD (g/cm²)	0.0069	0.0056, 0.0083	< 0.001	0.0025	−0.0131, 0.0136	NS	21.826	0.313

Linear and IV regression analysis of the relationships between BMD and percent body fat

Percent body fat (%)	Linear regression			IV regression				
	β	95% CI	P-value	β	95% CI	P-value	F-First*	WH P-value**
Total hip BMD (g/cm^2)	0.0035	0.0026, 0.0044	<0.001	0.0134	0.0019, 0.0250	0.023	17.188	0.067
Femoral neck BMD (g/cm^2)	0.0032	0.0024, 0.0040	<0.001	0.0094	0.0002, 0.0187	0.046	17.188	0.168
Total spine BMD (g/cm^2)	0.0013	0.0004, 0.0021	0.002	0.0013	-0.0079, 0.0104	0.784	17.090	0.997

Linear and IV regression analysis of the relationships between BMD and body fat mass

Body fat mass (kg)	Linear regression			IV regression				
	β	95% CI	P-value	β	95% CI	P-value	F-First*	WH P-value**
Total hip BMD (g/cm^2)	0.0052	0.0043, 0.0061	<0.001	0.0122	0.0023, 0.0221	0.016	15.378	0.142
Femoral neck BMD (g/cm^2)	0.0045	0.0041, 0.0055	<0.001	0.0086	0.0005, 0.0167	0.037	15.377	0.348
Total spine BMD (g/cm^2)	0.0026	0.0019, 0.0034	<0.001	0.0012	-0.0074, 0.0098	0.790	15.303	0.725

Conclusion

- The *FTO* polymorphism was significantly correlated with adiposity (BMI, BFM and PBF)
- An instrumental variable (IV) regression model, using adiposity as the intermediate phenotype, suggested that *FTO* was a strong IV.
- The *FTO*-BMI (FTO-BPF, and FTO-BFM) polymorphism was significantly associated with total hip and femoral neck BMDs but was not correlated with total spine
- Mendelian randomization approach suggests that adiposity might be causally related to bone mineral density at the femur but not at the spine.