Targeted Metabolomics Reveals an Influence of the FTO Gene on the Kynurenine Pathway

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Background:

The prevalence of obesity and overweight are increasing and is a worldwide health epidemic Obesity is a complex metabolic syndrome and its association with many chronic diseases. The development of obesity is influenced by a complex interaction between genetics and psychological factors. Several studies have shown an association between genes that are responsible for appetite control and lipid metabolism and obesity.

Genome wide association studies have identified the fat mass and obesity associated (FTO) gene as the first susceptibility gene of obesity. FTO is highly expressed in the hypothalamus, a region involved in the regulation of food intake and energy expenditure. Previous studies have suggested a role of FTO in nucleic acid repair or modification, but how this leads to an alteration in energy homeostasis is unclear. In the present study, we utilized targeted metabolomics in an attempt to further elucidate mechanisms underlying the action of the FTO gene.

Materials and methods:

This retrospective cross sectional study was part of a health survey of employees of the Electricity Generating Authority of Thailand in 2009 (n = 79, 9 female and 70 male), aged 30-54 years. Targeted metabolomics analysis was performed using the AbsoluteIDQ™ p180 kit (BIOCRATES Life Sciences AG, Innsbruck, Austria) combined with flow injection analysis and liquid chromatography tandem mass spectrometry. The assay quantifies up to 188 targeted metabolites covering the following 6 compound classes including 21 amino acids, 21 biogenic amines, 40 acylcarnitines, 90 glycerophospholipids, 15 sphingolipids and 1 hexoses. Genotyping of the FTO rs9939609 was performed using real-time PCR (TaqMan® MGB probes). Partial least-squares discriminant analysis (PLS-DA) was used to identify the features that discriminated between the groups. Statistical analysis and predictive models were conducted by using *ropls* package in Rstudio version 1.0.136 and R version 3.3.2.

Results:

Baseline characteristics of the study subjects grouped by the presence of the rs9939609 G allele are described in Table 1. Using PLS-DA, there was no apparent clustering of the metabolites in relation to the FTO genotype (Figure 1). Nevertheless, using variable importance in projection (VIP) to identify metabolites with higher influence on potential clustering, it was found that tryptophan was among the metabolites within the 10 highest VIP scores (Table 2). We therefore further examined the influence of the FTO gene on the major pathway of tryptophan catabolism, the kynurenine pathway. Pearson's correlation analysis showed that kynurenine and tryptophan was positively correlated only in subjects with the rs9939609 G allele (n = 32, r = 0.56, $p < 0.001$) and the correlation coefficients were significantly higher in subjects having the G allele compared to those subjects without the G allele (P < 0.05). Moreover, kynurenine/trytophan ratio, a biomarker of the degree of tryptophan to kynurenine conversion, was significantly associated with the presence of the G allele independent of body mass index and gender.

Conclusions:

FTO gene influences the conversion of tryptophan to kynurenine. Alternation in the kynurenine pathway may be one of the mechanisms underlying the action of FTO in the pathogenesis of obesity and its related effects.

Table 1. Baseline characteristics of the study subjects grouped by the presence of the rs9939609 G allele

Variables	rs9939609 G allele		
	Absence (n = 47)	Presence (n = 32)	*p* value
Age (year)	44.7 ± 6.7	42.2 ± 6.7	0.102
Male/Female	42/5	28/4	1.000
BMI (kg/m^2)	27.0 ± 4.7	27.2 ± 3.9	0.811
Tryptophan (μM)	85.4 ± 10.7	92.8 ± 10.8	0.003

Table 2. Metabolites with the 10 highest variable importance in projection (VIP) scores identified by PLS-DA

Metabolites Names	VIP scores
Tryptophan	2.39113652
Phosphatidylcholine acyl-alkyl C30:1	2.04376646
Lysophosphatidylcholine acyl C16:1	1.72065305
Tyrosine	1.58531222
Alanine	1.54157651
Phosphatidylcholine diacyl C32:0	1.47861492
Lysophosphatidylcholine acyl C20:3	1.44302942
Phosphatidylcholine acyl-alkyl C40:1	1.36549162
Phosphatidylcholine diacyl C36:0	1.26484546
Phosphatidylcholine diacyl C38:6	1.26221283

Cx:y = Total number of carbons and double bonds of all chains.

Figure 1. Score plot of partial least-squares discriminant analysis (PLS-DA). There was no significant separation the FTO genotype based on metabolites profile