CROSS SPECIES SURVEY STUDY OF POTENTIAL PHARMACOLOGICAL TARGETS FOR ANTI-OBESITY DRUGS

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Introduction

Obesity and obesity related conditions represent a leading public health problem in developed countries. Studies have shown that insulin resistance affiliated with obesity is associated with intramyocellular lipid (IMCL) accumulation.[1] Therefore, identification of genes associated with fat deposition would provide a promising target for pharmaceutical intervention and care for the condition. There are currently more than 600 loci in the human obesity gene map, comprising of gene candidates from animal models, association studies and QTL mapping experiments.[2] Here we review research on candidate genes that were shown to be associated with fat deposition by our studies and used comparative genomics approach for their further confirmation as potential pharmacological targets for anti-obesity drugs.

Material and methods

Genomic organization of cattle gene candidates for fat deposition was determined using in silico cloning approach and sequencing of their promoter- and coding regions. The developed markers were tested on an unique animal genetic resource, 250 Wagyu × Limousin F_2 progeny from the cross of two cattle breeds with extreme phenotypes informative for IMCL and subcutaneous fat depth (SFD) developed at Washington State University and USDA, ARS.

Results

Nine genes were associated with IMCL and/or SFD.[3–7] The candidate gene list and estimations of phenotypic effects of different alleles are presented in Table 1. All nine candidate genes reside in previously detected and published QTL regions/concordant QTL regions. For eight genes, involvement in fat associated traits was confirmed in other mammalian species (2,8, PubMed Database).

Table 1. *Genes associated with IMCL and/or SFD in Wagyu × Limousin F_2 progeny.*

Gene/ markers	IMCL (number of SNPs associated)	SFD (number of SNPs associated)	Gene in QTL/concordant QTL region	Cross species identification of fat associated traits
TFAM	3 (promoter)	2 (promoter)	SSC14	pig, mouse
UCN3	2* (exon 2)	4* (promoter)	HSA10p15.1	rat
FABP4	1	1	BTA14, SSC4	pig, mouse
PAPD1	–	2 (promoter)	HSA10p11.23	–
TG	–	1	BTA14	mouse
LEP	–	1 (exon 2)	HSA7q3, BTA4q	human, mouse
DGAT1	–	1	BTA14	mouse
GH1	–	1 (intron 3)	BTA19	human, mouse
FABP3	–	1	SSC6q	pig, mouse

TFAM: mitochondrial transcription factor A, *UCN3:* urocortin 3, *FABP4:* Fatty acid binding protein 4, *PAPD1:* mitochondrial poly(A) polymerase, *TG:* thyroglobulin, *LEP:* leptin, *DGAT:* Diacyglycerol O-acyltransferase 1, *GH1:* growth hormone 1, *FABP3:* fatty acid binding protein (heart) 3, *SNPs in linkage disequilibrium.

Conclusions

Our multi species survey study revealed evidence for nine genes that are involved in obesity related phenotypes and therefore could be proposed as potential targets for anti-obesity drug development.

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