Investigating the genetic regulation of the expression of 63 lipid metabolism genes in the pig skeletal muscle

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Abstract

Despite their potential involvement in the determination of fatness phenotypes, a comprehensive and systematic view about the genetic regulation of lipid metabolism genes is still lacking in pigs. Herewith, we have used a dataset of 104 pigs, with available genotypes for 62,163 single nucleotide polymorphisms and microarray gene expression measurements in the *gluteus medius* muscle, to investigate the genetic regulation of 63 genes with crucial roles in the uptake, transport, synthesis and catabolism of lipids. By performing an eQTL scan with the GEMMA software, we have detected 12 cis- and 18 trans-eQTL modulating the expression of 19 loci. Genes regulated by eQTL had a variety of functions such as the β -oxidation of fatty acids, lipid biosynthesis and lipolysis, fatty acid activation and desaturation, lipoprotein uptake, apolipoprotein assembly and cholesterol trafficking. These data provide a first picture about the genetic regulation of loci involved in porcine lipid metabolism.

Keywords: pigs, *gluteus medius*, gene expression, quantitative trait loci, lipid metabolism

Main text

The search of regulatory variants with causal effects on the expression of genes with important metabolic roles is fundamental to elucidate the genetic basis of multiple physiological and pathological phenotypes [1]. In humans, thousands of expression QTL (eQTL) have been detected so far and the majority of them appear to act locally (cis-eQTL) rather than influencing the expression of genes located at distant genomic regions or chromosomes (trans-eQTL) [1,2]. Moreover, around 50% of human cis-eQTL are shared across distinct tissues, though the consistency in the magnitude and the direction of these regulatory effects may be variable [2].

The genetic regulation of lipid metabolism genes has been poorly studied in pigs in spite of the fact that it may have a potential impact on the phenotypic variation of fatness traits. Indeed, the majority of eQTL studies performed in pigs have targeted either genes whose expression correlates with lipid phenotypes or loci comprised within the confidence intervals of fatness quantitative trait loci [3–7]. At present, we do not know if porcine lipid genes are predominantly regulated in cis- or trans- and if such regulation is featured by single or multiple polymorphisms. The goal of the current work was to shed light into these issues by identifying eQTL with effects on the muscle expression of 63 genes with an established role in the uptake, transport, synthesis and catabolism of lipids.

As animal material, we have used 104 barrows from a commercial Duroc porcine line (Lipgen population) distributed in five half-sib families. After weaning, this pig population was transferred to the experimental test station at the Centre de Control Porcí of the Institut de Recerca i Tecnologia Agroalimentàries (IRTA). A detailed description of the

experimental population and management conditions has been reported [8,9]. Barrows were slaughtered at an approximate age of 190 days. *Gluteus medius* (GM) muscle biopsies were obtained in the abattoir and they were immediately frozen in liquid nitrogen, being subsequently stored at -80 °C. All animal care and management procedures followed the ARRIVE guidelines [10] and they were approved by the Ethical Committee of the Institut de Recerca i Tecnologia Agroalimentàries (IRTA).

GeneChip Porcine Genomic arrays (Affymetrix, Inc., Santa Clara, CA) were used to measure gene expression in GM samples from the 104 Duroc pigs mentioned above (data are available in the Gene Expression Omnibus public repository of the National Center for Biotechnology Information, accession number: GSE19275). Data pre-processing and normalization were carried out with the BRB-ArrayTools software version 3.7.1.[11]. Genes displaying more than 20% of expression values over ± 1.5 times the median expression of all arrays were retained for further analysis. A detailed description of the techniques and methods used to perform RNA purification and microarray hybridization can be found in [12]. Finally, sixty three loci annotated in the Ensembl (S.scrofa 10.2) database and having a well established role in lipid metabolism (Supplementary Table 1) were selected for further analysis.

The Porcine SNP60K BeadChip (Illumina, San Diego, CA) was employed to genotype 62,163 single nucleotide polymorphisms (SNPs) in the 104 Duroc pigs by following a previously reported protocol [5]. The GenomeStudio software (Illumina) was employed to evaluate the quality of the typing data. By using PLINK [13], we discarded SNPs with rates of missing genotypes above 10%, minor allele frequencies (MAF) below 5%, as well as those did not conform Hardy-Weinberg expectations (threshold set at a P -

value of 0.001). Markers that did not map to the porcine reference genome (Sscrofa10.2 assembly) and those located in sex chromosomes were also eliminated from the data set. Moreover, were eliminated SNPs that were in complete linkage disequilibrium ($r^2 > 0.98$). After these filtering steps, a total of 28,571 SNPs were used to carry out a GWAS analysis for gene expression phenotypes.

Statistical analyses were performed with the GEMMA software [14] that uses a standard linear mixed model and an exact test of significance to identify associations between genotypes and phenotypes. The existence of population structure is taken into account by considering a relatedness matrix [14]. The model assumed in the statistical analysis was:

$$y_{ijklm} = \mu + batch_j + lab_k + \delta g_l + e_{ijklm}$$

where y_{ijklm} is the vector that describes the mRNA levels of each gene in the GM muscle of the i^{th} individual; μ is the mean mRNA expression of each gene in the population; $batch_j$ and lab_k are the systematic effects i.e. "batch of fattening" (with 4 categories) and "laboratory" (microarray data were produced in two distinct laboratories); δ is the SNP allelic effect estimated as a regression coefficient on the corresponding g_l genotype (values - 1, 0, 1) of the l^{th} SNP; and e_{ijklm} is the residual effect. Correction for multiple testing was implemented with a false discovery rate approach [15] and SNPs with a q-value ≤ 0.05 were considered as significantly associated with gene expression. In the analysis of cis-eQTL, multiple testing was corrected by taking into consideration the number of SNPs contained within 2 Mb windows around each gene, while in the trans-eQTL analysis we took into account the whole set of 28,571 SNPs.

The eQTL scan for lipid-related genes made possible to identify 12 cis-eQTL and 18 trans-eQTL influencing the mRNA levels of 19 loci (Tables 1 and 2, Figure 1). As shown in Table 1, the two cis-eQTL detected for the *ACOX3* (SSC8: 2.7-3.7 Mb and 4.4 Mb) and *NPC2* (SSC7: 102.5-103.1 Mb and 104.1-104.4 Mb) genes were located in adjacent positions and they might correspond to two genetic determinants (instead of 4). In a previous study, Chen et al. [16] identified 120 cis-eQTLs and 523 trans-eQTLs with effects on porcine hepatic gene expression. However, they focused their study on a dataset of 300-400 genes that showed significant correlations with traits under study and their sample size was larger than ours. In the current work, the numbers of cis- and trans-eQTL for lipid genes were quite similar (Tables 1 and 2). In contrast, Cánovas et al.[12] performed a genome scan for porcine muscle expression phenotypes and observed a predominance of trans- vs cis-eQTL. The most likely reason for this discrepancy is that we have used different thresholds of significance to correct for multiple testing in the cis- and trans-eQTL analyses. Indeed, in humans the majority of eQTL identified so far act in cis-. For instance, a recent eQTL scan in 869 lymphoblastoid cell lines revealed that 3,534 and 48 genes were affected by eQTL in cis- and trans-, respectively [17]. Similarly, a global analysis of 53 datasets demonstrated the existence of 116,563 high confidence eQTL [18]. Around 91% and 9% of these eQTL acted in cis- and trans-, respectively [18], and there was an average of 1.8 eQTL per gene.

The majority of trans-eQTL detected by us resided in chromosomes different than the one containing the targeted gene, suggesting that they may exert their effects through SNPs that alter the synthesis or structure of a diffusible factor. We also observed the existence of several genes (*e.g.* *ACADS* and *SLC25A17*) simultaneously regulated by eQTL in cis- and in trans- (Tables 1 and 2). Particularly relevant is the case of the *ACADS* gene,

whose expression was modulated by one and four cis- and trans-eQTL, respectively. This finding illustrates that even simple phenotypes, such as gene expression, can be regulated in a highly complex manner.

From a functional point of view, this set of 12 cis- and 18 trans-eQTL regulated the expression of genes integrated in distinct metabolic pathways. In this way, the acyl-coenzyme A dehydrogenases for short-chain (*ACADS*), medium-chain (*ACADM*) and long-chain (*ACADL*) FA catalyse the first step in the FA β -oxidation pathway, and the enoyl-CoA delta isomerase 2 (*ECI2*) gene plays an essential role in the β -oxidation of unsaturated FA. Moreover, the solute carrier family 25 member 17 (*SLC25A17*) gene encodes a peroxisomal transporter of coenzyme-A, FAD and NAD^+ cofactors [19] and it could have a role in the α -oxidation of FA [20]. We have also detected eQTL for genes comprised in lipid biosynthetic pathways (Tables 1 and 2). For instance, the glycerol-3-phosphate acyltransferase 3 (*GPAT3*) is involved in the synthesis of triacylglycerols [21], and the 3-hydroxy-3-methylglutaryl-CoA synthase 1 (*HMGCS1*) enzyme is a component of the cholesterol biosynthetic pathway [22]. Other relevant loci are the acyl-CoA synthetase family member 2 (*ACSF2*) gene, which may participate in FA activation [23], the *LACTB* gene that affects adiposity in mice females [23], the CCAAT/enhancer binding protein δ (*CEBPD*) gene that has a key role in the regulation of adipogenesis [24] and the Cbp/P300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 2 (*CITED2*) locus that is involved in the regulation of hepatic gluconeogenesis[25].

Conclusions

Our results demonstrate that around 30% of the lipid-related genes analysed in the current work are regulated by cis- and/or trans-eQTL with significant effects on their mRNA levels. In our data set, we have not detected a clear predominance of either cis- or trans-regulatory factors in the determination of gene expression, a result that contrasts with what has been obtained in humans where gene regulation is mostly exerted by cis-factors. In the next future, it would be worth to investigate if the set of eQTL detected herewith displays significant associations with the phenotypic variation of porcine traits of economic interest.

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Figure 1. Plots of cis-eQTLs (left panel) regulating *ACADS*, *SLC25A17* and *NPC2* mRNA levels and of trans-eQTLs (right panel) influencing the expression of the *ACADS*, *ACDL* and *ACFS2* loci. The x-axis represents the chromosomal region containing the eQTL (measured in Mb), and the y-axis shows the $-\log_{10}$ (P-value) of the associations found. The horizontal line indicates the threshold of significance ($q\text{-value} \leq 0.05$). Vertical lines in left panel plots depict the genomic location of the *ACADS*, *SLC25A17* and *NPC2* genes.

Table 1. Cis-eQTLs regulating the expression of 10 genes involved in porcine lipid metabolism¹.

Genes			Cis-eQTL									
Symbol	SSC	Location (Mb)	SSC	N	SNP	Region (Mb)	P-value	q-value	B	$\delta \pm SE$	A1	MAF
<i>ACADS</i>	14	43.1	14	34	MARC0094155	42.6-45.9	0.00	0.00	0.00	-0.62 ± 0.08	A	0.21
<i>ACOX3</i>	8	4.3-4.4	8	1	ALGA0118448	4.4	0.00	0.00	0.00	-0.75 ± 0.18	A	0.08
				2	M1GA0025674	2.7-3.7	0.00	0.02	0.03	-0.34 ± 0.10	A	0.36
<i>CITED2</i>	1	28.2	1	4	MARC0028659	26.5-27.4	0.01	0.02	0.07	0.27 ± 0.10	A	0.38
<i>HMGCS1</i>	16	29.4	16	18	ALGA0089927	28.0-29.8	0.01	0.02	0.14	0.23 ± 0.07	G	0.35
<i>LRP6</i>	5	63.5-63.6	5	20	ASGA0025668	62.2-63.8	0.00	0.02	0.13	0.42 ± 0.13	A	0.40
<i>LIPA</i>	14	110.1	14	10	ASGA0065584	108.8-109.9	0.01	0.04	0.14	0.27 ± 0.11	G	0.19
<i>NCOA1</i>	3	121.2-121.3	3	3	MARC0003746	120.0-120.4	0.00	0.02	0.05	-0.28 ± 0.08	A	0.27
<i>NPC2</i>	7	103.5	7	3	INRA0027651	104.1-104.4	0.00	0.01	0.04	0.28 ± 0.09	A	0.28
				6	ALGA0043923	102.5-103.1	0.00	0.00	0.00	0.33 ± 0.07	A	0.26
<i>SLC25A17</i>	5	4.8	5	27	H3GA0015347	2.7-5.9	0.00	0.00	0.00	-0.79 ± 0.15	G	0.30
<i>VLDLR</i>	1	245.0	1	1	ASGA0005756	244.9	0.00	0.04	0.04	-0.33 ± 0.13	A	0.20

¹SSC: porcine chromosome, N: Number of SNPs significantly associated with traits under study, SNP: SNPs displaying the most significant associations with traits under study, Region (Mb): regions containing SNPs significantly associated with traits under study, P-value: nominal P-value, q-value: q-value calculated with a false discovery rate approach, B : Bonferroni-corrected P-value, δ : allelic effect and its standard error (SE), A1: minority allele, MAF: frequency of the minority allele.

Table 2. Trans-eQTLs regulating the expression of 12 genes involved in porcine lipid metabolism¹.

Genes			Trans-eQTLs									
Symbol	SSC	Location (Mb)	SSC	N	SNP	Region (Mb)	P-value	q-value	B	$\delta \pm SE$	A1	MAF
<i>ACADL</i>	15	124.7-124.7	3	1	MARC0017993	144.3-144.3	0.00	0.03	0.08	-0.58 ± 0.13	A	0.18
				2	ALGA0123606	21.7-21.8	0.00	0.03	0.07	-0.58 ± 0.13	A	0.18
<i>ACADM</i>	6	127.5-127.5	13	7	DIAS0003141	141.6-144.1	0.00	0.04	0.21	-0.72 ± 0.15	A	0.12
			9	1	MARC0004327	29.5-29.5	0.00	0.04	0.34	-0.56 ± 0.12	A	0.22
<i>ACADS</i>	14	43.1-43.1	17	1	INRA0053259	28.7-28.7	0.00	0.05	0.97	-0.46 ± 0.09	A	0.45
			14	3	H3GA0040210	53.7-55.5	0.00	0.00	0.02	-0.48 ± 0.08	G	0.28
			12	3	M1GA0017106	58.9-59.4	0.00	0.02	0.24	-0.54 ± 0.12	G	0.12
			3	1	MARC0039787	134.6-134.6	0.00	0.01	0.19	-0.47 ± 0.11	G	0.18
<i>ACSF2</i>	12	26.8-26.8	12	4	MARC0030253	33.2-34.0	0.00	0.01	0.09	-0.49 ± 0.10	A	0.50
<i>APOA1</i>	9	49.2-49.2	1	3	MARC0004843	181.0-183.7	0.00	0.01	0.01	1.02 ± 0.19	G	0.07
<i>CEBPD</i>	4	87.3-87.3	7	1	ALGA0045624	128.5-128.5	0.00	0.04	0.04	1.30 ± 0.25	G	0.04
<i>CMIP</i>	6	7.1-7.2	5	2	ASGA0103424	12.4-12.7	0.00	0.04	0.36	0.59 ± 0.13	G	0.06
			13	7	DIAS0003141	141.6-144.1	0.00	0.00	0.00	0.58 ± 0.09	A	0.12
<i>ECI2</i>	7	2.5-2.5	12	1	MARC0021670	37.0-37.0	0.00	0.03	0.03	-0.62 ± 0.13	G	0.16
<i>GPAT3</i>	8	144.2-144.2	17	1	H3GA0049617	61.6-61.6	0.00	0.05	0.18	0.65 ± 0.14	G	0.22
<i>LACTB</i>	1	120.1-120.1	15	2	MARC0020666	3.2-3.4	0.00	0.05	0.08	-0.62 ± 0.14	A	0.13
<i>LRP6</i>	5	63.5-63.6	4	1	MARC0056621	134.9-134.9	0.00	0.03	0.03	-0.42 ± 0.08	G	0.47
<i>SLC25A17</i>	5	4.8-4.8	1	7	SIRI0000355	129.2-138.3	0.00	0.03	0.26	-0.64 ± 0.13	A	0.18

¹SSC: porcine chromosome, N: Number of SNPs significantly associated with traits under study, SNP: SNPs displaying the most

significant associations with traits under study, Region (Mb): regions containing SNPs significantly associated with traits under study,

P-value: nominal P-value, q-value: q-value calculated with a false discovery rate approach, B : Bonferroni-corrected P-value, δ : allelic

effect and its standard error (SE), A1: minority allele, MAF: frequency of the minority allele.

Supplementary Table 1. List of 63 lipid-related genes analysed in the current work.

Ensembl ID	Name	Acronym
ENSSSCG00000026173	ATP-binding cassette, sub-family A (ABC1), member 1	<i>ABCA1</i>
ENSSSCG00000028620	ATP-binding cassette, sub-family D (ALD), member 3	<i>ABCD3</i>
ENSSSCG00000016156	acyl-CoA dehydrogenase, long chain	<i>ACADL</i>
ENSSSCG00000003776	acyl-CoA dehydrogenase, C-4 to C-12 straight chain	<i>ACADM</i>
ENSSSCG00000009916	acyl-CoA dehydrogenase, C-2 to C-3 short chain	<i>ACADS</i>
ENSSSCG00000008724	acyl-CoA oxidase 3, pristanoyl	<i>ACOX3</i>
ENSSSCG00000017566	acyl-CoA synthetase family member 2	<i>ACSF2</i>
ENSSSCG00000015784	acyl-CoA synthetase long-chain family member 1	<i>ACSL1</i>
ENSSSCG00000016223	acyl-CoA synthetase long-chain family member 3	<i>ACSL3</i>
ENSSSCG00000012583	acyl-CoA synthetase long-chain family member 4	<i>ACSL4</i>
ENSSSCG00000000757	adiponectin receptor 2	<i>ADIPOR2</i>
ENSSSCG00000005829	1-acylglycerol-3-phosphate O-acyltransferase 2	<i>AGPAT2</i>
ENSSSCG00000015755	1-acylglycerol-3-phosphate O-acyltransferase 5	<i>AGPAT5</i>
ENSSSCG00000013599	angiopoietin like 4	<i>ANGPTL4</i>
ENSSSCG00000030921	apolipoprotein A1	<i>APOA1</i>
ENSSSCG00000003088	apolipoprotein E	<i>APOE</i>
ENSSSCG00000016634	caveolin 1, caveolae protein, 22kDa	<i>CAV1</i>
ENSSSCG00000016635	caveolin 2	<i>CAV2</i>
ENSSSCG00000006276	CCAAT/enhancer binding protein (C/EBP), delta	<i>CEBPD</i>
ENSSSCG00000010449	cholesterol 25-hydroxylase	<i>CH25H</i>
ENSSSCG00000004142	Cbp/p300-interacting transactivator, with Glu/Asp rich carboxy-terminal domain, 2	<i>CITED2</i>
ENSSSCG00000002689	c-Maf inducing protein	<i>CMIP</i>
ENSSSCG00000015391	carnitine O-octanoyltransferase	<i>CROT</i>
ENSSSCG00000006126	2,4-dienoyl CoA reductase 1, mitochondrial	<i>DECR1</i>
ENSSSCG00000003854	enoyl CoA hydratase domain containing 2	<i>ECHDC2</i>
ENSSSCG00000001000	enoyl-CoA delta isomerase 2	<i>ECI2</i>
ENSSSCG00000026044	farnesyl-diphosphate farnesyltransferase 1	<i>FDFT1</i>
ENSSSCG00000010631	glycerol-3-phosphate acyltransferase, mitochondrial	<i>GPAM</i>

ENSSSCG00000008569	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase , beta subunit	<i>HADHB</i>
ENSSSCG00000016379	high density lipoprotein binding protein	<i>HDLBP</i>
ENSSSCG00000016872	3-hydroxy-3-methylglutaryl-CoA synthase 1 (soluble)	<i>HMGCS1</i>
ENSSSCG00000026025	3-hydroxymethyl-3-methylglutaryl-CoA lyase	<i>HMGCL</i>
ENSSSCG00000016420	insulin induced gene 1	<i>INSIG1</i>
ENSSSCG00000010226	jumonji domain containing 1C	<i>JMJD1C</i>
ENSSSCG00000004569	lactamase beta	<i>LACTB</i>
ENSSSCG00000010450	lipase A, lysosomal acid, cholesterol esterase	<i>LIPA</i>
ENSSSCG00000003018	lipase, hormone-sensitive	<i>LIPE</i>
ENSSSCG00000004509	lipase, endothelial	<i>LIPG</i>
ENSSSCG00000000625	low density lipoprotein receptor-related protein 6	<i>LRP6</i>
ENSSSCG00000028960	lanosterol synthase (2,3-oxidosqualene-lanosterol cyclase)	<i>LSS</i>
ENSSSCG00000016918	mitogen-activated protein kinase kinase kinase 1, E3 ubiquitin protein ligase	<i>MAP3K1</i>
ENSSSCG00000004454	malic enzyme 1, NADP(+)-dependent, cytosolic	<i>ME1</i>
ENSSSCG00000024134	monoglyceride lipase	<i>MGLL</i>
ENSSSCG00000025447	MID1 interacting protein 1	<i>MID1IP1</i>
ENSSSCG00000001063	myosin regulatory light chain interacting protein	<i>MYLIP</i>
ENSSSCG00000008581	nuclear receptor coactivator 1	<i>NCOA1</i>
ENSSSCG00000003707	Niemann-Pick disease, type C1	<i>NPC1</i>
ENSSSCG00000002366	Niemann-Pick disease, type C2	<i>NPC2</i>
ENSSSCG00000016863	3-oxoacid CoA transferase 1	<i>OXCT1</i>
ENSSSCG00000011215	3-oxoacyl-ACP synthase, mitochondrial	<i>OXSM</i>
ENSSSCG00000001539	peroxisome proliferator-activated receptor delta	<i>PPARD</i>
ENSSSCG00000011579	peroxisome proliferator-activated receptor gamma	<i>PPARG</i>
ENSSSCG00000003837	protein kinase, AMP-activated, alpha 2 catalytic subunit	<i>PRKAA2</i>
ENSSSCG00000000185	protein kinase, AMP-activated, gamma 1 non-catalytic subunit	<i>PRKAG1</i>
ENSSSCG00000016432	protein kinase, AMP-activated, gamma 2 non-catalytic subunit	<i>PRKAG2</i>
ENSSSCG00000026281	SREBF chaperone	<i>SCAP</i>
ENSSSCG00000009759	scavenger receptor class B, member 1	<i>SCARB1</i>
ENSSSCG00000010554	stearoyl-CoA desaturase (delta-9-	<i>SCD</i>

	desaturase)	
ENSSSCG00000010116	solute carrier family 25 (mitochondrial carrier	<i>SLC25A1</i>
ENSSSCG00000000072	solute carrier family 25 (mitochondrial carrier	<i>SLC25A17</i>
ENSSSCG00000015232	ST3 beta-galactoside alpha-2,3-sialyltransferase 4	<i>ST3GAL4</i>
ENSSSCG00000017402	signal transducer and activator of transcription 5A	<i>STAT5A</i>
ENSSSCG00000005229	very low density lipoprotein receptor	<i>VLDLR</i>