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# Detection of quantitative trait loci affecting serum cholesterol, LDL, HDL, and triglyceride in pigs

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## Abstract

**Background:** Serum lipids are associated with many serious cardiovascular diseases and obesity problems. Many quantitative trait loci (QTL) have been reported in the pig mostly for performance traits but very few for the serum lipid traits. In contrast, remarkable numbers of QTL are mapped for serum lipids in humans and mice. Therefore, the objective of this research was to investigate the chromosomal regions influencing the serum level of the total cholesterol (CT), triglyceride (TG), high density protein cholesterol (HDL) and low density protein cholesterol (LDL) in pigs. For this purpose, a total of 330 animals from a Duroc × Pietrain F2 resource population were phenotyped for serum lipids using ELISA and were genotyped by using 122 microsatellite markers covering all porcine autosomes for QTL study in QTL Express. Blood sampling was performed at approximately 175 days before slaughter of the pig.

**Results:** Most of the traits were correlated with each other and were influenced by average daily gain, slaughter date and age. A total of 18 QTL including three QTL with imprinting effect were identified on 11 different porcine autosomes. Most of the QTL reached to 5% chromosome-wide (CW) level significance including a QTL at 5% experiment-wide (GW) and a QTL at 1% GW level significance. Of these QTL four were identified for both the CT and LDL and two QTL were identified for both the TG and LDL. Moreover, three chromosomal regions were detected for the HDL/LDL ratio in this study. One QTL for HDL on SSC2 and two QTL for TG on SSC11 and 17 were detected with imprinting effect. The highly significant QTL (1% GW) was detected for LDL at 82 cM on SSC1, whereas significant QTL (5% GW) was identified for HDL/LDL on SSC1 at 87 cM. Chromosomal regions with pleiotropic effects were detected for correlated traits on SSC1, 7 and 12. Most of the QTL identified for serum lipid traits correspond with the previously reported QTL for similar traits in other mammals. Two novel QTL on SSC16 for HDL and HDL/LDL ratio and an imprinted QTL on SSS17 for TG were detected in the pig for the first time.

**Conclusion:** The newly identified QTL are potentially involved in lipid metabolism. The results of this work shed new light on the genetic background of serum lipid concentrations and these findings will be helpful to identify candidate genes in these QTL regions related to lipid metabolism and serum lipid concentrations in pigs.

**Keywords:** pig, QTL, serum lipids, F2 population

## Background

Cholesterol (CT) is a lipid present in the cell membranes and transported in the bloodstream of all animals. CT is important for the synthesis of cell membrane and hormones and play vital role in the cell signaling process [1]. Cholesterol concentration in high density lipoprotein (HDL) and low density lipoprotein (LDL) are strong predictors for coronary heart disease and obesity. Higher

concentration of LDL cholesterol and lower concentration of functional HDL are strongly associated with cardiovascular disease due to high risk of atherosclerosis [2]. LDL particles accumulated on the vessel walls to form lipid cores and cause inflammation that promotes atherosclerosis [3]. Triglyceride (TG) is the main constituent in vegetable oil and animal fat. The high level of triglyceride in the bloodstream is also linked to atherosclerotic heart disease [4] and pancreatitis [5]. The existence of a relevant amount of additive genetic variability for serum lipid traits in pigs has been demonstrated by Rothschild and

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Chapman [6] and Pond *et al.* [7], and subsequently corroborated in several divergent selection experiments [8,9].

The current release of the Pig QTLdb (<http://www.animalgenome.org/cgi-bin/QTLdb/SS/viewmap>) contains 5621 quantitative trait loci (QTL) representing 546 different traits (December, 2010) mostly for economically important traits like growth, carcass and meat quality, and reproduction. However, only two studies have so far been reported which have scanned the chromosomal regions influencing the serum lipid levels in pig. The first report of QTL for serum lipids [10] suggested a number of significant QTL in Duroc outbred populations including two genome-wide significant QTL for HDL/LDL ratio (at 84 cM on SSC6) and for TG (at 23 cM on SSC4). Another study reported a total of 15 QTL including five novel QTL for serum lipids in a White Duroc × Erhualian intercross F2 population [11]. Hasler-Rapacz *et al.* [12] reported a locus on SSC2 linked to familial hypercholesterolemia in a Duroc group and showed the low-density-lipoprotein receptor gene (*LDLR*) as the candidate gene. In contrast, over the past two decades, lots of QTL have been identified in livestock, model organisms and human. Numerous QTL for serum lipids have been widely studied in human [13] and mice [14] such as QTL for TG which has been detected on every murine chromosome [15], and QTL for HDL on the mouse and human genomes are near “saturated” due to the concordance between the two species [16]. Moreover, beside as a source of food, the pig has tremendous biomedical importance as a model organism because of its closer proximity to human than most of the animal models including mice. The pig has the same size as humans as well as high anatomic and physiological similarities [17] and has the ability to be used in xenotransplantation [18]. The origin and distribution of the coronary arteries as well as the histological changes of growth and aging that apparently lead to atherosclerosis of aortas and coronary arteries in humans and pigs are also closely similar [19]. The common pathogenesis of atherosclerotic lesions in both humans and pigs [12] implies that pig could be the appropriate model for human atherosclerosis research. QTL study in different species, breeds and populations will deepen our understanding of the genetics behind lipid metabolism. The identified chromosomal regions will facilitate the identification of the potential candidate genes responsible for serum lipid concentrations in pigs which could be beneficial for human cardiovascular disease research. Therefore, the aim of this study was to identify the chromosomal regions affecting serum lipoproteins (TG, HDL, LDL, HDL/LDL and cholesterol) concentrations in a F2 Duroc × Pietrain resource population.

## Results

### Phenotypic variation of serum lipid traits

The descriptive statistics of the serum lipids traits measured in a Duroc × Pietrain (DUPI) F2 population are given in Table 1. The CT and HDL/LDL ratio was significantly correlated ( $P < 0.001$ ) with all other traits. HDL also had significant correlation with TG levels. The HDL/LDL ratio was negatively correlated with CT ( $r = -0.42$ ) and LDL ( $r = -0.69$ ) concentration (Table 1). The GLM procedure in SAS allows dissection of the effects of genetic and environmental factors on these traits. Slaughter date, average daily gain (ADG) and age at slaughter significantly ( $P < 0.001$ ) influenced the CT, HDL and LDL concentrations, whereas slaughter date and ADG had effect ( $P < 0.01$ ) on TG concentrations. Only slaughter date had significant ( $P < 0.001$ ) effect on the traits HDL/LDL ratio. This study could not detect any statistical significant effect of sex and litter size on any serum lipid traits.

### QTL results for serum lipid traits

A total of 18 QTL were identified in 11 different autosomes, of which one QTL was highly significant ( $P < 0.01$ ) at experiment-wide (GW) level, one QTL was significant (GW;  $P < 0.05$ ), 15 QTL were suggestive ( $P < 0.05$ ) at chromosome-wide (CW) level and only one QTL for TG on SSC2 was very close to the suggestive level with LOD 1.98 (Table 2). Most of the identified QTL showed higher additive effect. Interestingly, we identified a putative pleiotropic QTL region on SSC1 between the markers *S3012* and *SW2166* influencing the CT, LDL and HDL/LDL traits. The most significant QTL of this study was found for LDL concentrations ( $F$  value = 12.63) at 82 cM in this region on SSC1 explaining 8.12% of the phenotypic variations of the LDL concentrations. The GW significant QTL for HDL/LDL found at 87 cM on the same chromosomal region explained up to 5.78% of trait variances (Figure 1a). Two other possible pleiotropic QTL regions were detected at 70 cM on SSC7 (Figure 1b) and at 36-38 cM on SSC12 for CT and LDL concentration (Figure 1c). On SSC12, a suggestive chromosomal region was found (5%, CW) influencing the CT concentration close to the marker *S0143* and contributed 5.21% of the trait variation. The suggestive (5% CW) QTL regions were identified at 0 cM on SSC3 for HDL, at 58 cM on SSC4 for HDL/LDL ratio and two regions on SSC6 at 66 cM and 99 cM for TG and CT, respectively.

The imprinting model revealed three imprinted QTL regions, a QTL for HDL on SSC2 (close to the marker *SW240*), and two QTL for TG on SSC11 (close to the marker *S0071*) and on SSC17 (close to the marker *SW2431*). QTL for HDL on SSC2 and for TG on SSC17

**Table 1 Descriptive statistics, correlation coefficient (above diagonal) and significance (below diagonal) of serum lipid traits**

Traits <sup>a</sup>	N	Mean ± SD <sup>b</sup>	Minimum	Maximum	CT	HDL	TG	LDL	HDL/LDL
CT	330	81.18 ± 12.79	50.95	110.94		0.31	0.22	0.83	-0.42
HDL	330	23.68 ± 4.59	12.19	34.53	***		0.22	0.10	0.59
TG	330	40.18 ± 11.96	15.04	74.10	***	***		0.06	0.10
LDL	330	49.46 ± 11.26	25.53	78.12	***	NS	NS		-0.69
HDL/LDL	330	0.49 ± 0.14	0.21	1.28	***	***	***	***	

<sup>a</sup>Trait abbreviations: CT Cholesterol concentrations (mg/dL); HDL High Density Lipoprotein concentrations (mg/dL); TG Triglyceride concentrations (mg/dL); LDL Low Density Lipoprotein concentrations (mg/dL); HDL/LDL ratio between HDL and LDL concentrations, N = number of animals; NS not significant.

<sup>b</sup>Standard deviation; \*\*\*  $P < 0.001$ .

were paternally imprinted (maternally expressed) while the QTL for TG on SSC11 was maternally imprinted (paternally expressed) in this study (Table 2).

## Discussion

### Serum lipid concentrations

Despite being an excellent animal model for cholesterol related human diseases, the genetic architecture of serum lipids is not well understood in pigs [10]. The heritability of serum lipid traits are recorded from low

to medium, for instance 0.22 for cholesterol levels [6], 0.18 to 0.30 for serum lipid concentrations [20]. The serum lipid concentrations can vary among breeds and age at sampling as shown by our results of serum lipid values which at 175 days in DUP1 was slightly higher than the values recorded at 45 days but lower than the values recorded at 190 days of age in Duroc populations [10]. It has been reported in humans that serum lipid concentrations could vary with age [21]. Moreover, our results were close to the serum lipid concentrations

**Table 2 Summary of QTL for the serum lipid traits**

SSC <sup>a</sup>	Traits <sup>b</sup>	POS <sup>c</sup>	F-value <sup>d</sup>	LOD	Var <sup>e</sup> (%)	a <sup>f</sup> ± SE	d <sup>g</sup> ± SE	Closest Markers <sup>h</sup>
1	CT	80	5*	2.14	3.38	3.2 ± 1.01	0.22 ± 1.5	S0312 - SW2166
1	HDL/LDL	87	8.74**	3.69	5.78	-0.05 ± 0.01	0 ± 0.02	S0312 - SW2166
1	LDL	82	12.63***	5.26	8.12	4.62 ± 0.93	-0.94 ± 1.44	S0312 - SW2166
2	TG	205	4.64	1.98	3.14	-3.13 ± 1.03	-0.05 ± 1.62	SW1884 - SWR308
2	HDL <sup>#</sup>	118	4.44*	2.83	4.47	-0.03 ± 0.37	1.31 ± 0.59	SW240 - SW1564
3	HDL	0	4.54*	1.94	3.08	0.73 ± 0.37	-1.11 ± 0.52	SW72 - S0164
4	HDL/LDL	58	4.53*	1.94	3.08	-0.04 ± 0.01	-0.01 ± 0.02	S0001 - S0214
6	CT	99	5.73*	2.44	3.85	0.92 ± 1.01	-5.15 ± 1.63	S0059 - S0003
6	TG	66	4.5*	1.93	3.05	-2.91 ± 0.98	0.37 ± 1.53	S0087 - SW1067
7	CT	70	5.15*	2.2	3.48	2.74 ± 0.89	-1.41 ± 1.32	Sw175 - S0115
7	LDL	70	5*	2.13	3.38	2.52 ± 0.81	-0.67 ± 1.19	Sw175 - S0115
11	TG <sup>#</sup>	28	4.64*	2.96	4.66	-1.02 ± 0.98	0.61 ± 1.36	SW2008 - S0071
12	CT	36	7.86**	3.32	5.21	5.27 ± 1.63	-9.89 ± 4.03	S0143 - SW874
12	LDL	38	4.8*	2.05	3.25	3.86 ± 1.49	-6.6 ± 3.66	S0143 - SW874
13	LDL	97	6.17*	2.62	4.14	-0.17 ± 0.87	-4.76 ± 1.36	TNNC - SW398
16	HDL	81	4.51*	1.93	3.06	-1.28 ± 0.46	-1.25 ± 0.81	SW0026 - S0061
16	HDL/LDL	47	4.55*	1.95	3.09	-0.05 ± 0.02	-0.08 ± 0.04	S0111 - SW0026
17	TG <sup>#</sup>	72	4.44*	2.83	4.46	1.37 ± 1.52	9.67 ± 4.24	SW840 - SW2431

<sup>a</sup>Sus scrofa chromosome

<sup>b</sup>See Table 1

<sup>c</sup>Chromosomal position in Kosambi cM

<sup>d</sup>Significance of the QTL: \* significant on a chromosome-wide level with  $P < 0.05$ ; \*\* significant on a experiment-wide level with  $P < 0.05$ ; \*\*\* significant on a experiment-wide level with  $P < 0.01$

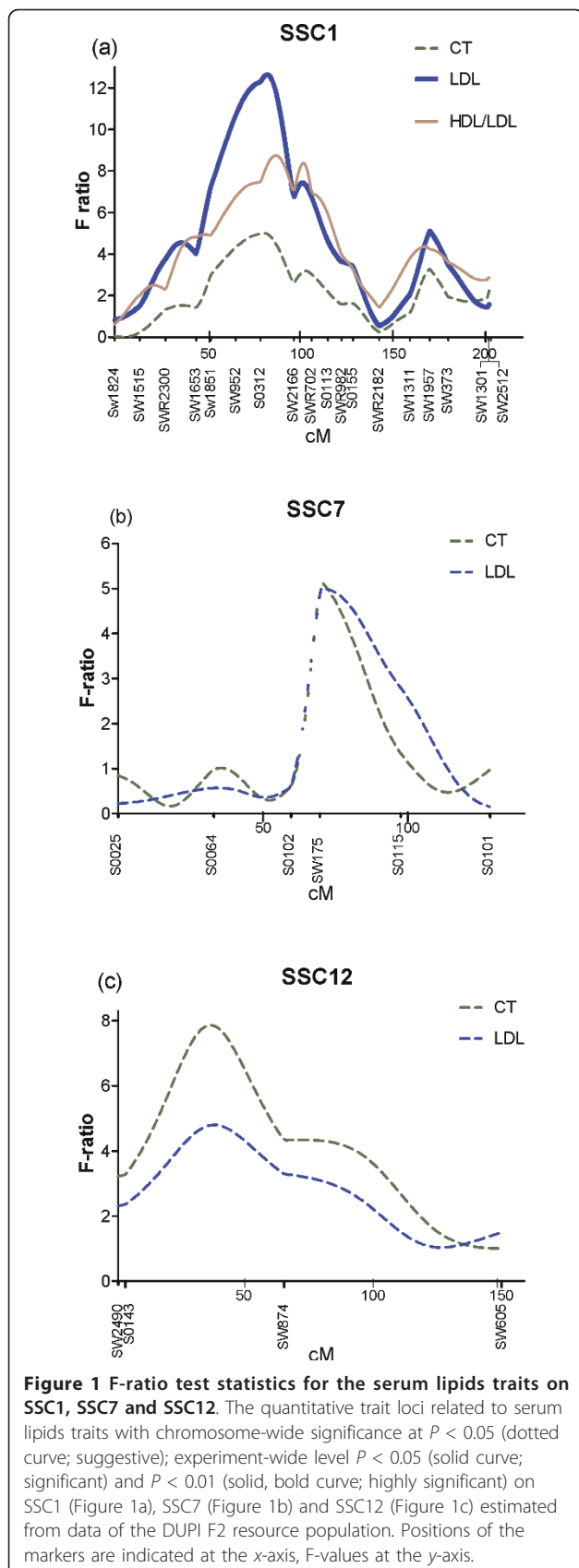
<sup>e</sup>The percentage of phenotypic variance explained by the QTL

<sup>f</sup>Additive effect and standard error. Positive values indicate the Duroc alleles result in higher values than Pietrain alleles; negative values indicate that Duroc alleles result in lower values than Pietrain alleles

<sup>g</sup>Dominance effect and standard error

<sup>h</sup>The closest markers were those markers around the peak, as near as possible (position of markers in cM)

<sup>#</sup> The imprinting effect and standard error was detected for HDL (1.03 ± 0.38) on SSC2, for TG (-3.18 ± 0.9) on SSC11 and for TG (-4.6 ± 1.58) on SSC17. When both the additive and the imprinting effects are positive or negative, the paternal allele expresses (maternal imprinting); otherwise the maternal allele expresses (paternal imprinting)



reported in White Duroc and Erhualian crossbred population [11]. HDL, LDL and TG are all involved in lipid or cholesterol metabolism which supports our results since these traits were found to be highly positively correlated to each other (Table 1). We also found that HDL/LDL ratios are negatively correlated with CT and LDL which is in good agreement with previous report in pigs [10] for serum sampled at 190 days of age.

Serum lipid traits are known as quantitative traits which are influenced by both genetic and non genetic factors [6]. In the present study, slaughter date had influence on all the traits, and age at slaughter and average daily gain (ADG) were influencing the CT, LDL and HDL/LDL ratio in this study. Animals were fasted overnight before slaughter, which might affect the animal physiology and circulation system since Chen *et al.* [11] also reported that batches were affected the serum lipid traits. The impact of age at slaughter date on serum lipid concentrations is consistent with the previous report [10] that in pigs the serum lipid concentration is age-dependent. Sex is reported to have significant influence on the serum levels by several different studies in pigs [6,11,22] but in this study sex did not have any significant effect on serum lipids which is in accordance with Rothschild and Cahpman [6]. However, we found only slight difference in cholesterol concentrations between male and female animals in which males tended to have higher cholesterol concentrations compared to female (data not shown).

#### QTL for serum lipid traits

Most of our identified QTL displayed high additive effect but still there were some over dominance QTL (Table 2). Duroc and Pietrain crosses are a good model for muscle and carcass trait studies [23,24] since Duroc and Pietrain are divergent for these traits [25]. However, to our knowledge, no such report is found with regards to serum lipid traits. It has been reported that the Duroc-sired pigs have more backfat and total fat tissues whereas the Pietrain-sired pigs have less backfat and total fat tissues [25]. Due to the unavailability of serum samples from pure breeds it was not possible for us to measure the serum lipid concentration in Duroc and Pietrain separately. The dominant QTL are difficult to explain since there are no reports about heterosis for serum lipid traits. Moreover, the low number of animals and family structure [23] of our F2 population should be considered. However, the existence of a relevant amount of additive genetic variability for serum lipid traits in pigs has been demonstrated by several studies [6-9] and some QTL for serum lipid traits with over dominance effect are also reported in pigs [11]. The genetic landscape of the QTL for serum lipid traits has been extensively investigated in humans, rats (<http://rgd.mcw.edu/>) and mice (<http://rgd.mcw.edu/>)

[www.informatics.jax.org/](http://www.informatics.jax.org/)); but there are very few studies devoted to studying QTL for serum lipids in pigs. Most of our QTL are supported by homologous QTL regions recorded in other mammals (Table 3), especially in humans and mice. Detection of common QTL regions for similar traits among mammals could contribute to narrowing down the confidence regions that affect plasma lipid traits and subsequently to find positional

candidate genes for cholesterol-related diseases such as heart disease, obesity and diabetes.

The most significant QTL found in the present study was the QTL for LDL at 82 cM on SSC1 (Table 2) which coincided with a QTL for ADG and two QTL for back fat thickness in pigs [26]. Moreover, in the same resource population, Liu *et al.* [23] found a 1% GW significance level QTL for ADG at 93 cM, supporting our

**Table 3 Comparative positional analysis of identified QTL with serum lipid QTL in humans and mice and the putative candidate genes located on the QTL regions**

SSC	Traits	POS (cM)	PCB at peak	HCHR	QTL in human	HCBP	Putative candidate genes	Mouse strain	QTL mouse peak
1	CT*	80	1q1.3 - 1.4	18q21 15q21-22	CT	18q21 [51]	<i>LIPC</i> [52], <i>LIPG</i> [53], <i>ACAA2</i> [54], <i>STARDB6</i> [55]	(B6 × C3H) F <sub>2</sub> (B6 × DBA/2) F <sub>2</sub> (B6 × CAST/2) F <sub>2</sub> (B6 × C3H) F <sub>2</sub> (B6 × 129) F <sub>2</sub>	18-40cM 18-46cM 18-47cM 18-48cM 2-90 cM
1	HDL/ LDL**	87	1q1.5-1.6		HDL	15q21 [56], 15q22 [57]			
1	LDL***	82	1q1.3 - 1.4		LDL-ApoB1	18q21.32 [58]			
2	TG	205	2q2.8-2.9	5q23-31	TG	5 q21.3 -q32 [59]	<i>STARDB4</i> [60]		
2	HDL*#	118	2p1.2- 2q1.2	11q13	HDL	11q12-13 [31]	<i>CILP</i> , <i>PBX4</i>	(MRL × SJL) F <sub>2</sub> (B6 × C3H) F <sub>2</sub>	7-10 cM 7-19 cM
3	HDL*	0	3p1.5-p1.4	7q11	HDL TC	7q11.23 [61] 7q11.23 [62]	<i>FABP1</i>	(NZB × SM) F <sub>2</sub> NZO × (SJL × NZO) F <sub>2</sub> (B6 × CAST) F <sub>2</sub>	5-61.cM 5-69cM 5-72 CM
4	HDL/ LDL*	58	4q1.4-1.5	1q22-25	HDL	1q21-23 [63] 1q23-25 [64]; 1q24 [65], 1q25 [66]	<i>CYP7A1</i> [67,68]; <i>FABP5</i> [69]	(B6 × NZB11) F <sub>2</sub>	1-91 CM
6	CT*	99	6q2.3 - 2.4	1p36.3-36.1	LDL	1q36.31 [63] 1q36.13 [70]	<i>NR1H2</i> <i>WVVOX</i> [71] <i>LDLRAP1</i>		
6	TG*	66	6q1.1 - 2.1	19q13	LDL, TG	19 q12 39 cM [72] 19q13.31 [51], [73]	<i>APOE</i> [74]; <i>ANGPTL3</i>		
7	CT, LDL*	70	7q1.4-71.5	15q24-28	LDL	15q26.1 [51]	<i>STARDB5</i>		
11	TG*#	28	11p1.1 -1.2	13q12 -24	TG and HDL	13q13 [75]			
12	CT**	36	12p1.3-q1.2	17q21-25	CT/HDL	17q24 [76]	<i>WIPI1</i> ,		
12	LDL*	38			LDL	17q24.2 [65]; 17q25.3 [77]	<i>THRA</i> <i>PEMT</i>		
13	LDL*	97	13q3.3 -3.5	3p31-21	LDL	3p25 [72]	<i>PCYT1A</i> [78]; <i>B4GALT4</i> [79]	(C56BL/6J × DBA/2J)	3-27cM [80]
16	HDL*	81	16q1.4-2.1	5p14 -12	HDL	5p13.3 [81] 5p15.13 [82]		(PERAX/DBA/2) F <sub>2</sub> (PERAXI) F <sub>2</sub>	11-28 cM 11-28 cM
16	HDL/ LDL*	47	16q1.3-1.4	5p14 -12	LDL	5p15.33 [64]			
17	TG*#	72	17q2.2-2.3	13q13	TG and HDL	13q13 [75]	<i>ACSS</i> , <i>PLTP</i>		

PCB, pig cytogenetic band; HCHR, human chromosome homologous regions; HCBP, human cytogenetic band.

Significance: Significance of the QTL: \* significant on a chromosome-wide level with  $P < 0.05$ ; \*\* significant on a experiment-wide level with  $P < 0.05$ ; \*\*\* significant on a experiment-wide level with  $P < 0.01$ . Human homologous regions of the pig QTL were identified with the pig QTL database. # QTL with imprinting effect.



findings that average daily weight gain is correlated to serum lipid levels. Gallardo *et al.* [10] also found a 1% CW significant QTL for LDL and a suggestive QTL for HDL/LDL ratio on SSC1. Additionally, we found a suggestive QTL for CT and a significant (5% GW) QTL for HDL/LDL ratio in this narrow region. These findings indicated that there are pleiotropic genes underlying this region affecting both fat and serum lipid concentrations in pigs. It is important to note that SSC1 was genotyped by 18 informative markers in this study which was advantageous to detect the peak of QTL with regards to markers (Figure 1a). This QTL region contained several potential candidate genes for serum lipid traits including endothelial lipase (*LIPG*), hepatic lipase (*LIPC*) and *ACAA2* in humans and *Stard6* in mice (Table 3). *LIPC* and *LIPG* are the members of lipase family genes and play significant roles in cholesterol metabolism especially in plasma HDL metabolism [27]. The *LIPC* gene encodes hepatic triglyceride lipase and has the capacity to catalyze the hydrolysis of phospholipids, mono-, di- and triglycerides [28]. Moreover, the promoter variant in *LIPC* is reported to be associated with elevated serum HDL cholesterol in humans and the variants of this gene are also associated with plasma HDL [29]. Animals that over express *LIPG* are reported to show decreased HDL cholesterol levels and those lacking *LIPG* show elevated levels of HDL cholesterol [30]. Furthermore, this region is homologous to human chromosome HSA18q21 and HSA15q21 harbouring QTL for CT and QTL for HDL in humans (Table 3). The region is also homologous with a 40 - 48 cM region on mouse chromosome 18 (*MUS18*) where a number of QTL for HDL are reported at 40, 46, 47 and 48 cM in different strains [31].

We found a QTL region for TG at 205 cM on SSC2q2.8-2.9 which was very close to the suggestive level and the confidence interval of this QTL overlaps with the previously reported QTL for TG in pigs [11]. This region is homologous with the QTL region for TG on HSA5q21.3-32 (Table 3). Moreover, a paternally imprinted QTL for HDL is identified at 118 cM very approximate to the marker *SW240* on SSC2 and very close to this region Liu *et al.* [23] reported a imprinting QTL for backfat thickness in the same population. A remarkable number of imprinting QTL have been identified on SSC2 (<http://igc.otago.ac.nz/>) such as imprinting QTL for backfat thickness [32] and average backfat [33] in pigs. *IGF2* which is reported to have strong imprinting effects on muscle mass and fat deposition [34], is located on SSC2 within the confidence interval of our identified imprinting QTL region for HDL on SSC2. Kadlecova *et al.* [35] suggested that polymorphism in the *IGF2* gene might have effects on lipid metabolism in rats. Moreover, the *IGF2* gene is reported to play a central role in atherosclerosis in a

mouse model [36]. A suggestive QTL for HDL is identified at 0 cM on SSC3 and close to this region, Gallardo *et al.* [10] reported QTL for cholesterol at 27 cM and 15 cM, and for HDL at 28 cM in pigs. This region corresponds to HSA7q11 that showed a consistent association with atherosclerosis disease in human [37]. It has been well established that HDL-cholesterol is the key member of the reverse transport process of cholesterol flowing from peripheral tissue to the liver in mammals and is greatly negatively associated with atherosclerotic disease [11]. A suggestive chromosomal region for HDL/LDL ratio was detected at the pericentromeric region on SSC4 in this study (Table 2). HDL/LDL cholesterol ratio is reported to be an excellent predictor to assess the risk of heart disease and to monitor the effectiveness of lipid lowering therapies [38]. The peak QTL region harbors fatty acid binding protein 5 (*FABP5*) on SSC4 which is known to have functions in lipid metabolism; the knockdown of *FABP5* decreased the cellular cholesterol (Table 3). The cholesterol 7 alpha-hydroxylase (*CYP7A1*) gene is also located in our region of interest on SSC4 and is reported to be responsible for coding a rate-limiting enzyme in the synthesis of bile acid from cholesterol. Moreover, several studies revealed the association of this gene with the plasma LDL levels in humans (Table 3).

Two neighbour QTL regions on SSC6 were identified for TG and CT within 33 cM very close to the marker *SW1067* and *S0059*, respectively. Apolipoprotein E (*ApoE*) is an important gene for the HDL metabolism and is located within the confidence interval of these QTL on SSC6. This gene contributes more to normal cholesterol variability than any other gene identified in cholesterol metabolism [39]. A QTL in the corresponding region on HSA19q13 influenced both the TG levels and adiposity in human (Table 3). Close to the marker *SW175*, a possible pleiotropic QTL for both the LDL and CT is found on SSC7 at 70 cM in this study (Figure 1b). LDL and CT were positively ( $r = 0.83$ ,  $P < 0.001$ ) correlated in the studied population. Pleiotropic QTL for HDL and CT close to the marker *SW632* are also identified by Gallardo *et al.* [10] in Duroc populations. This QTL region is homologous to HAS15q26 affecting the LDL in humans (Table 3). A suggestive QTL for CT was identified at 38 cM on SSC12 and contributes 5.2% of phenotypic variation of total cholesterol (Table 2). Two cM apart from this QTL, another suggestive QTL was found for LDL (Figure 1c), which can be assumed as a possible pleiotropic QTL in this study. For these two QTL, alleles that increase phenotypic variation were inherited from the Duroc breed. Gallardo *et al.* [10] also found a QTL for TG and HDL/LDL ratio very close to our identified region on SSC12. Corresponding to this region, HSA17q24 is reported to influence the plasma CT and HDL in humans (Table 3).

This study identified a suggestive QTL for LDL at 97 cM on SSC13 (Table 2). Based on the identified QTL for HDL, CT, LDL and HDL/LDL ratio with pleiotropic effects between 72-79 cM in Duroc pigs, Gallardo *et al.* [10] speculated to have several interesting loci such as phosphate cytidyltransferase 1, choline,  $\alpha$ -isoform (*PCYT1A*) and the UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide4 (*B4GALT4*) in this region (Table 3). In this study, two novel QTL were identified on SSC16 for HDL at 81 cM and HDL/LDL ratio at 47 cM, which are homologous to HSA5q31 and HSA5p14-12, respectively. QTL for HDL is reported on HSA5p13.3 and HSA5p15.13 in humans (Table 3). To the best of our knowledge, the identified pig genomic regions influencing the serum lipid concentration are described for the first time. A novel imprinting QTL for TG at 72 cM is detected on SSC17 in this study (Table 2) and several imprinted QTL have been reported in this chromosomal region such as QTL for longissimus fat content, marbling [40] and for average daily gain [33] in pigs.

## Conclusions

The results of this work enrich genetic landscapes of serum lipid traits in pigs. Since cholesterol, lipoproteins and triglyceride are considered as strong predictors for atherosclerosis disease, the identification of the QTL regions influencing these traits is an important step for understanding the genetics behind and to scan for the candidate genes related to serum lipid-related diseases. However, before addressing the candidate genes in the identified QTL regions, it is important to note that the confidence intervals of the QTL were large and could contain many genes affecting the serum lipid traits. The SSC1q1.3-q1.6 region harbouring significant QTL for serum lipid traits requires fine mapping to detect potential candidate genes in this region. Two novel QTL regions on SSC16 for lipoprotein traits have been identified and are worthwhile of further research.

## Methods

### Resource population

The animal population used for the evaluation of serum lipoprotein traits included three generations (P, F1 and F2) of Duroc  $\times$  Pietrain family as described earlier [23,24,41,42]. A total of 330 F2 pigs were used in this study. All animals were kept at the Frankenforst experimental research farm at the University of Bonn (Germany) according to the rules of German performance stations (Zentralverband der Deutschen Schweineproduktion (ZDS): Richtlinie für die Stationsprüfung auf Mastleistung, Schlachtkörperwert und Fleischbeschaffenheit beim Schwein, 10.12.2003). The F2 pigs were fed the same diet *ad libitum* during the whole test period and were

slaughtered at approximately 105 kg live weight at around the age of 25 weeks. Samples from the tail were collected within the first week after birth for DNA isolation. Blood samples were taken at approximately 175 days of age before slaughter with fasting but free access to overnight. Serum was isolated from blood and stored at  $-80^{\circ}\text{C}$  until use.

### Measurement of lipoproteins levels

All serum lipid traits were assayed by ELISA according to the manufacturer's procedure (BioAssay Systems, USA) and read at 570 nm by ELISA Plate Reader (DYNEX Technologies, Inc, USA). In brief, total cholesterol and TG concentrations were measured using Enzy Chrom<sup>TM</sup> cholesterol assay kit (cat. E2CH-100) and Enzy Chrom<sup>TM</sup> triglyceride assay kit (cat. ETGA-200), respectively. The slopes used for the calculation of CT and TG levels were determined by linear regression fitted using serial diluted concentrations. 10  $\mu\text{L}$  of serum samples and 50  $\mu\text{L}$  of working reagent were added to 96 well plates. The plates were tapped well and incubated for 30 minutes at room temperature before reading the optical density (OD). The CT and TG concentrations were calculated based on the slopes of the standard line, OD value of samples and blank according to the manufacturer's formula. For HDL measurement, colorimetric procedure using Enzy-Chrom<sup>TM</sup> HDL and LDL/VLDL Assay Kit (cat. EHDL-100) was used. Briefly, equal volume (20  $\mu\text{L}$ ) of serum and precipitation reagent were mixed by vortexing. After centrifugation, 24  $\mu\text{L}$  of the supernatant was pipetted carefully into a clean tube and 96  $\mu\text{L}$  assay buffer was added. Then, equal amount (50  $\mu\text{L}$ ) of the mixture, assay buffer and cholesterol standard were transferred separately into 96-well plates. Finally, 50  $\mu\text{L}$  of working reagent was added to each well. The plates were then tapped well and read at 570 nm in ELISA plate reader. HDL concentrations were calculated from OD of sample, blank and standards following manufacturer's formula. LDL concentrations were calculated following Freide-wald's formula (mg/dL) [43].

### Statistical analysis

The data were analysed using the SAS software package version 9.2 (SAS Institute Inc., Cary, NC, USA) for a detailed description of the data structure. Descriptive statistics and correlations among these traits were calculated by the PROC MEANS and PROC CORR procedures (Table 1). Generalised linear models (PROC GLM) were used to identify any possible effect of sire, dam, sex, average daily weight gain, ages at slaughter, slaughter date and litter size on the serum lipid concentrations. The phenotypic data followed approximately a normal distribution and were used for linkage analysis.

### Marker analysis

A linkage map with the total length of 2159.3 cM and an average marker interval of 17.7 cM was constructed [42]. P, F1 and F2 animals of the Duroc × Pietrain (DUPI) population were genotyped previously [23], [44] at 122 markers loci covering all porcine autosomes. Marker positions and details of genotyping procedures were given in Liu *et al.* [23] and for SSC1 in Grosse-Brinkhaus *et al.* [44]. These markers were mainly selected from the USDA/MARC map (<http://www.marc.usda.gov>) and most are available in Sscrofa5 ([http://www.ncbi.nlm.nih.gov/projects/mapview/map\\_search.cgi?taxid=9823](http://www.ncbi.nlm.nih.gov/projects/mapview/map_search.cgi?taxid=9823)) and Sscrofa9 ([http://www.ensembl.org/Sus\\_sscrofa/Info/Index](http://www.ensembl.org/Sus_sscrofa/Info/Index)). Genotyping, electrophoresis, and allele determination were done using a LI-COR 4200 Automated Sequencer including the software OneDScan (Scanalytics). The CE8000 sequencer (Beckman Coulter, USA) was used for genotyping of SSC1 and SSC18. Allele and inheritance genotyping errors were checked using Pedcheck software (version 1.1) [45]. The relative positions of the markers were assigned using the build, twopoint and fixed options of CRIMAP software (version 2.4) [46]. Recombination units were converted to map distances using the Kosambi mapping function. Marker information content and segregation distortion were tested by following Knott *et al.* [47].

### QTL analysis

F2 QTL interval mapping was performed using the web-based program QTL Express [48] based on a least square regression method. Single-QTL analyses were carried out and imprinting model was also applied. The basic QTL regression model used in the present study was:

$$y_i = \mu + F_i + \beta \text{cov}_i + c_{ai}a + c_{di}d + \varepsilon_i$$

where:  $y_i$  = phenotype of the  $i^{\text{th}}$  offspring;  $\mu$  = overall mean;  $F_i$  = Fixed effect (slaughter date,  $i$  from 1 to 40);  $\beta$  = regression coefficient on the covariate;  $\text{cov}_i$  = covariate (average daily weight gain and age at slaughter (in days) were covariates for CT, HDL and LDL; average daily weight gain was covariates for TG; and HDL/LDL ratio had no covariate);  $c_{ai}$  = additive coefficient of the  $i^{\text{th}}$  individual at a putative QTL in the genome;  $c_{di}$  = dominant coefficient of the  $i^{\text{th}}$  individual at a putative QTL in the genome;  $a$  = additive effects of a putative QTL;  $d$  = dominant effects of a putative QTL; and  $\varepsilon_i$  = residual error.

The presence of imprinting effects was tested by adding a third (imprinting) effect ( $i$ ) into the model [47] using QTL Express [48]. Chromosome- (CW) and experiment-wide (GW) significance thresholds were determined using 1000 permutations [49]. The empirical

95% confidence intervals (CI) and flanking markers for the QTL positions were obtained with 1000 re-sampling steps [50]. The phenotype variation that was explained by a QTL was calculated by the following equation.

$$\text{Var}\% = \frac{MS_R - MS_F}{MS_R} \times 100$$

Where,  $MS_R$  is the mean of square of the reduced model,  $MS_F$  is the mean of square of the full model.

To identify positional candidate genes underlying QTL, syntenic regions corresponding to QTL were defined by integrated comparative RH map at <http://animalgenome.org/cgi-bin/QTLdb/SS/viewmap>, and candidate genes were determined via the UCSC Genome Browser (<http://genome.ucsc.edu/cgi-bin/hgGateway>).

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### Authors' contributions

MJU and DND performed the experiments, analysed data and prepared and edited the manuscript. MUC arranged the experiment facilities and edited the manuscript. HJ was responsible for sampling. DT, ET and CL edited the manuscript with MJU and DND. KS criticized the experimental design, supervised this study and edited the manuscript. All authors read and approved the final manuscript.

### Competing interests

The authors declare that there is no competing financial or other interest in relation to this work.

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### References

1. Burger K, Gimpl G, Fahrenholz F: Regulation of receptor function by cholesterol. *Cell Mol Life Sci* 2000, **57**(11):1577-1592.
2. Howard BV, Robbins DC, Sievers ML, Lee ET, Rhoades D, Devereux RB, Cowan LD, Gray RS, Welty TK, Go OT, *et al*: LDL cholesterol as a strong predictor of coronary heart disease in diabetic individuals with insulin resistance and low LDL: The Strong Heart Study. *Arterioscler Thromb Vasc Biol* 2000, **20**(3):830-835.
3. Libby P: Inflammation in atherosclerosis. *Nature* 2002, **420**(6917):868-874.
4. Austin MA: Plasma triglyceride and coronary heart disease. *Arterioscler Thromb* 1991, **11**(1):2-14.
5. Yadav D, Pitchumoni CS: Issues in hyperlipidemic pancreatitis. *J Clin Gastroenterol* 2003, **36**(1):54-62.
6. Rothschild MF, Cahprman AB: Factors influencing serum cholesterol levels in swine. *J Hered* 1976, **67**(1):47-48.
7. Pond WG, Mersmann HJ, Young LD: Heritability of plasma cholesterol and triglyceride concentrations in swine. *Proc Soc Exp Biol Med* 1986, **182**(2):221-224.
8. Harris KB, Pond WG, Mersmann HJ, Smith EO, Cross HR, Savell JW: Evaluation of fat sources on cholesterol and lipoproteins using pigs selected for high or low serum cholesterol. *Meat Science* 2004, **66**(1):55-61.
9. Lu CD, Pond WG, Mersmann HJ, Su DR, Krook L, Harris JJ, Savell JW: Response to dietary fat and cholesterol in young adult boars genetically selected for high or low plasma cholesterol. *J Anim Sci* 1995, **73**(7):2043-2049.



10. Gallardo D, Pena RN, Amills M, Varona L, Ramirez O, Reixach J, Diaz I, Tibau J, Soler J, Prat-Cuffi JM, et al: **Mapping of quantitative trait loci for cholesterol, LDL, HDL, and triglyceride serum concentrations in pigs.** *Physiol Genomics* 2008, **35**(3):199-209.
11. Chen R, Ren J, Li W, Huang X, Yan X, Yang B, Zhao Y, Guo Y, Mao H, Huang L: **A genome-wide scan for quantitative trait loci affecting serum glucose and lipids in a White Duroc × Erhualian intercross F(2) population.** *Mamm Genome* 2009, **20**(6):386-392.
12. Hasler-Rapacz J, Ellegren H, Fridolfsson AK, Kirkpatrick B, Kirk S, Andersson L, Rapacz J: **Identification of a mutation in the low density lipoprotein receptor gene associated with recessive familial hypercholesterolemia in swine.** *Am J Med Genet* 1998, **76**(5):379-386.
13. Aberg K, Sun G, Smelser D, Indugula SR, Tsai HJ, Steele MS, Tuitele J, Deka R, McGarvey ST, Weeks DE: **Applying novel genome-wide linkage strategies to search for loci influencing type 2 diabetes and adult height in American Samoa.** *Hum Biol* 2008, **80**(2):99-123.
14. Herrera VL, Didishvili T, Lopez LV, Myers RH, Ruiz-Opazo N: **Genome-wide scan identifies novel QTLs for cholesterol and LDL levels in F2[Dahl R×S]-intercross rats.** *Circ Res* 2004, **94**(4):446-452.
15. Stylianou IM, Langley SR, Walsh K, Chen Y, Revenu C, Paigen B: **Differences in DBA/1J and DBA/2J reveal lipid QTL genes.** *J Lipid Res* 2008, **49**(11):2402-2413.
16. Wang X, Paigen B: **Genetics of variation in HDL cholesterol in humans and mice.** *Circ Res* 2005, **96**(1):27-42.
17. Miller ER, Ullrey DE: **The pig as a model for human nutrition.** *Annu Rev Nutr* 1987, **7**:361-382.
18. Yang YG, Sykes M: **Xenotransplantation: current status and a perspective on the future.** *Nat Rev Immunol* 2007, **7**(7):519-531.
19. Ratcliffe HL, Luginbuhl H: **The domestic pig: a model for experimental atherosclerosis.** *Atherosclerosis* 1971, **13**(1):133-136.
20. Casellas J, Noguera JL, Reixach J, Diaz I, Amills M, Quintanilla R: **Bayes factor analyses of heritability for serum and muscle lipid traits in Duroc pigs.** *J Anim Sci* **88**(7):2246-2254.
21. Snieder H, van Doornen LJ, Boomsma DI: **Dissecting the genetic architecture of lipids, lipoproteins, and apolipoproteins: lessons from twin studies.** *Arterioscler Thromb Vasc Biol* 1999, **19**(12):2826-2834.
22. Misaki Kojima MSaMD: **Gender-Related Differences in the Level of Serum Lipids in Meishan Pigs.** *J Health Sci* 2008, **54**:97-100.
23. Liu G, Jennen DG, Tholen E, Juengst H, Kleinwachter T, Holker M, Tesfaye D, Un G, Schreinemachers HJ, Murani E, et al: **A genome scan reveals QTL for growth, fatness, leanness and meat quality in a Duroc-Pietrain resource population.** *Anim Genet* 2007, **38**(3):241-252.
24. Liu G, Kim JJ, Jonas E, Wimmers K, Ponsuksili S, Murani E, Phatsara C, Tholen E, Juengst H, Tesfaye D, et al: **Combined line-cross and half-sib QTL analysis in Duroc-Pietrain population.** *Mamm Genome* 2008, **19**(6):429-438.
25. Edwards DB, Tempelman RJ, Bates RO: **Evaluation of Duroc- vs. Pietrain-sired pigs for growth and composition.** *J Anim Sci* 2006, **84**(2):266-275.
26. de Koning DJ, Pong-Wong R, Varona L, Evans GJ, Giuffra E, Sanchez A, Plastow G, Noguera JL, Andersson L, Haley CS: **Full pedigree quantitative trait locus analysis in commercial pigs using variance components.** *J Anim Sci* 2003, **81**(9):2155-2163.
27. Yasuda T, Ishida T, Rader DJ: **Update on the role of endothelial lipase in high-density lipoprotein metabolism, reverse cholesterol transport, and atherosclerosis.** *Circ J* 2010, **74**(11):2263-2270.
28. Connelly PW, Hegele RA: **Hepatic lipase deficiency.** *Crit Rev Clin Lab Sci* 1998, **35**(6):547-572.
29. Tahvanainen E, Sivanne M, Frick MH, Murtomaki-Repo S, Antikainen M, Kesaniemi YA, Kauma H, Pasternak A, Taskinen MR, Ehnholm C: **Association of variation in hepatic lipase activity with promoter variation in the hepatic lipase gene. The LOCAT Study Investigators.** *J Clin Invest* 1998, **101**(5):956-960.
30. Jaye M, Lynch KJ, Krawiec J, Marchadier D, Maugeais C, Doan K, South V, Amin D, Perrone M, Rader DJ: **A novel endothelial-derived lipase that modulates HDL metabolism.** *Nat Genet* 1999, **21**(4):424-428.
31. Rollins J, Chen Y, Paigen B, Wang X: **In search of new targets for plasma high-density lipoprotein cholesterol levels: promise of human-mouse comparative genomics.** *Trends Cardiovasc Med* 2006, **16**(7):220-234.
32. de Koning DJ, Rattink AP, Harlizius B, van Arendonk JA, Brascamp EW, Groenen MA: **Genome-wide scan for body composition in pigs reveals important role of imprinting.** *Proc Natl Acad Sci USA* 2000, **97**(14):7947-7950.
33. Thomsen H, Lee HK, Rothschild MF, Malek M, Dekkers JC: **Characterization of quantitative trait loci for growth and meat quality in a cross between commercial breeds of swine.** *J Anim Sci* 2004, **82**(8):2213-2228.
34. Nezer C, Moreau L, Brouwers B, Coppieters W, Detilleux J, Hanset R, Karim L, Kvasz A, Leroy P, Georges M: **An imprinted QTL with major effect on muscle mass and fat deposition maps to the IGF2 locus in pigs.** *Nat Genet* 1999, **21**(2):155-156.
35. Kadlecova M, Dobesova Z, Zicha J, Kunes J: **Abnormal Igf2 gene in Prague hereditary hypertriglyceridemic rats: its relation to blood pressure and plasma lipids.** *Mol Cell Biochem* 2008, **314**(1-2):37-43.
36. Zaina S, Pettersson L, Ahren B, Branen L, Hassan AB, Lindholm M, Mattsson R, Thyberg J, Nilsson J: **Insulin-like growth factor II plays a central role in atherosclerosis in a mouse model.** *J Biol Chem* 2002, **277**(6):4505-4511.
37. Arya R, Duggirala R, Almay L, Rainwater DL, Mahaney MC, Cole S, Dyer TD, Williams K, Leach RJ, Hixson JE, et al: **Linkage of high-density lipoprotein-cholesterol concentrations to a locus on chromosome 9p in Mexican Americans.** *Nat Genet* 2002, **30**(1):102-105.
38. Fernandez ML, Webb D: **The LDL to HDL cholesterol ratio as a valuable tool to evaluate coronary heart disease risk.** *J Am Coll Nutr* 2008, **27**(1):1-5.
39. Sing CF, Davignon J: **Role of the apolipoprotein E polymorphism in determining normal plasma lipid and lipoprotein variation.** *Am J Hum Genet* 1985, **37**(2):268-285.
40. Rohrer GA, Thallman RM, Shackelford S, Wheeler T, Koohmaria M: **A genome scan for loci affecting pork quality in a Duroc-Landrace F population.** *Anim Genet* 2006, **37**(1):17-27.
41. Uddin MJ, Cinar MU, Grosse-Brinkhaus C, Tesfaye D, Tholen E, Juengst H, Looft C, Wimmers K, Phatsara C, Schellander K: **Mapping quantitative trait loci for innate immune response in the pig.** *Int J of Immunogenet* 2011, **38**:121-131.
42. Uddin MJ, Grosse-Brinkhaus C, Cinar MU, Jonas E, Tesfaye D, Tholen E, Juengst H, Looft C, Ponsuksili S, Wimmers K, et al: **Mapping of quantitative trait loci for mycoplasma and tetanus antibodies and interferon-gamma in a porcine F(2) Duroc × Pietrain resource population.** *Mamm Genome* 2010, **21**(7-8):409-418.
43. Friedewald WT, Levy RI, Fredrickson DS: **Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge.** *Clin Chem* 1972, **18**(6):499-502.
44. Grosse-Brinkhaus PC, Tholen E, Schellander K, J E: **Feinkartierung von qtl für fleischqualitätsmerkmale auf dem porcinen chromosom 1.** *Züchtungskunde* 2009, **81**:63-68.
45. O'Connell JR, Weeks DE: **PedCheck: a program for identification of genotype incompatibilities in linkage analysis.** *Am J Hum Genet* 1998, **63**(1):259-266.
46. Green PK, Falls a, Crooks S: **Documentation for CRIMAP, Version 2.4.** Washington University School of Medicine, St Louis, MO; 1990.
47. Knott SA, Marklund L, Haley CS, Andersson K, Davies W, Ellegren H, Fredholm M, Hansson I, Hoyheim B, Lundstrom K, et al: **Multiple marker mapping of quantitative trait loci in a cross between outbred wild boar and large white pigs.** *Genetics* 1998, **149**(2):1069-1080.
48. Seaton G, Haley CS, Knott SA, Kearsey M, Visscher PM: **QTL Express: mapping quantitative trait loci in simple and complex pedigrees.** *Bioinformatics* 2002, **18**(2):339-340.
49. Churchill GA, Doerge RW: **Empirical threshold values for quantitative trait mapping.** *Genetics* 1994, **138**(3):963-971.
50. Visscher PM, Thompson R, Haley CS: **Confidence intervals in QTL mapping by bootstrapping.** *Genetics* 1996, **143**(2):1013-1020.
51. Bosse Y, Chagnon YC, Despres JP, Rice T, Rao DC, Bouchard C, Perusse L, Vohl MC: **Genome-wide linkage scan reveals multiple susceptibility loci influencing lipid and lipoprotein levels in the Quebec Family Study.** *J Lipid Res* 2004, **45**(3):419-426.
52. Guerra R, Wang J, Grundy SM, Cohen JC: **A hepatic lipase (LIPC) allele associated with high plasma concentrations of high density lipoprotein cholesterol.** *Proc Natl Acad Sci USA* 1997, **94**(9):4532-4537.
53. Hutter CM, Austin MA, Farin FM, Viernes HM, Edwards KL, Leonetti DL, McNeely MJ, Fujimoto WY: **Association of endothelial lipase gene (LIPG) haplotypes with high-density lipoprotein cholesterol subfractions and**

- apolipoprotein AI plasma levels in Japanese Americans. *Atherosclerosis* 2006, **185**(1):78-86.
54. Kathiresan S, Melander O, Guiducci C, Surti A, Burt NP, Rieder MJ, Cooper GM, Roos C, Voight BF, Havulinna AS, et al: **Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans.** *Nat Genet* 2008, **40**(2):189-197.
55. Ning Y, Xu L, Ren S, Pandak WM, Chen S, Yin L: **StAR overexpression decreases serum and tissue lipids in apolipoprotein E-deficient mice.** *Lipids* 2009, **44**(6):511-519.
56. Feitosa MF, Province MA, Heiss G, Arnett DK, Myers RH, Pankow JS, Hopkins PN, Borecki IB: **Evidence of QTL on 15q21 for high-density lipoprotein cholesterol: the National Heart, Lung, and Blood Institute Family Heart Study (NHLBI FHS).** *Atherosclerosis* 2007, **190**(1):232-237.
57. Almasy L, Hixson JE, Rainwater DL, Cole S, Williams JT, Mahaney MC, VandeBerg JL, Stern MP, MacCluer JW, Blangero J: **Human pedigree-based quantitative-trait-locus mapping: localization of two genes influencing HDL-cholesterol metabolism.** *Am J Hum Genet* 1999, **64**(6):1686-1693.
58. Bosse Y, Chagnon YC, Despres JP, Rice T, Rao DC, Bouchard C, Perusse L, Vohl MC: **Compendium of genome-wide scans of lipid-related phenotypes: adding a new genome-wide search of apolipoprotein levels.** *J Lipid Res* 2004, **45**(12):2174-2184.
59. Falchi M, Andrew T, Snieder H, Swaminathan R, Surdulescu GL, Spector TD: **Identification of QTLs for serum lipid levels in a female sib-pair cohort: a novel application to improve the power of two-locus linkage analysis.** *Hum Mol Genet* 2005, **14**(20):2971-2979.
60. Soccio RE, Adams RM, Romanowski MJ, Sehayek E, Burley SK, Breslow JL: **The cholesterol-regulated StarD4 gene encodes a StAR-related lipid transfer protein with two closely related homologues, StarD5 and StarD6.** *Proc Natl Acad Sci USA* 2002, **99**(10):6943-6948.
61. Lehman DM, Arya R, Blangero J, Almasy L, Puppala S, Dyer TD, Leach RJ, O'Connell P, Stern MP, Duggirala R: **Bivariate linkage analysis of the insulin resistance syndrome phenotypes on chromosome 7q.** *Hum Biol* 2005, **77**(2):231-246.
62. Sonnenberg GE, Krakower GR, Martin LJ, Olivier M, Kwitek AE, Comuzzie AG, Blangero J, Kissebah AH: **Genetic determinants of obesity-related lipid traits.** *J Lipid Res* 2004, **45**(4):610-615.
63. Elbein SC, Hasstedt SJ: **Quantitative trait linkage analysis of lipid-related traits in familial type 2 diabetes: evidence for linkage of triglyceride levels to chromosome 19q.** *Diabetes* 2002, **51**(2):528-535.
64. Coon H, Leppert MF, Eckfeldt JH, Oberman A, Myers RH, Peacock JM, Province MA, Hopkins PN, Heiss G: **Genome-wide linkage analysis of lipids in the Hypertension Genetic Epidemiology Network (HyperGEN) Blood Pressure Study.** *Arterioscler Thromb Vasc Biol* 2001, **21**(12):1969-1976.
65. Broeckel U, Hengstenberg C, Mayer B, Holmer S, Martin LJ, Comuzzie AG, Blangero J, Nurnberg P, Reis A, Riegger GA, et al: **A comprehensive linkage analysis for myocardial infarction and its related risk factors.** *Nat Genet* 2002, **30**(2):210-214.
66. Adeyemo AA, Johnson T, Acheampong J, Oli J, Okafor G, Amoah A, Owusu S, Agyenim-Boateng K, Eghan BA Jr, Abbiyesuku F, et al: **A genome wide quantitative trait linkage analysis for serum lipids in type 2 diabetes in an African population.** *Atherosclerosis* 2005, **181**(2):389-397.
67. Couture P, Otvos JD, Cupples LA, Wilson PW, Schaefer EJ, Ordovas JM: **Association of the A-204C polymorphism in the cholesterol 7alpha-hydroxylase gene with variations in plasma low density lipoprotein cholesterol levels in the Framingham Offspring Study.** *J Lipid Res* 1999, **40**(10):1883-1889.
68. Kovar J, Suchanek P, Hubacek JA, Poledne R: **The A-204C polymorphism in the cholesterol 7alpha-hydroxylase (CYP7A1) gene determines the cholesterolemia responsiveness to a high-fat diet.** *Physiol Res* 2004, **53**(5):565-568.
69. Wu T, Tian J, Cutler RG, Telljohann RS, Bernlohr DA, Mattson MP, Handa JT: **Knockdown of FABP5 mRNA decreases cellular cholesterol levels and results in decreased apoB100 secretion and triglyceride accumulation in ARPE-19 cells.** *Lab Invest* 2010, **90**(6):963-965.
70. Reed DR, Nanthakumar E, North M, Bell C, Price RA: **A genome-wide scan suggests a locus on chromosome 1q21-q23 contributes to normal variation in plasma cholesterol concentration.** *J Mol Med* 2001, **79**(5-6):262-269.
71. Saez ME, Gonzalez-Perez A, Martinez-Larrad MT, Gayan J, Real LM, Serrano-Rios M, Ruiz A: **WVVOX gene is associated with HDL cholesterol and triglyceride levels.** *BMC Med Genet* 11:148.
72. Pollin TI, Hsueh WC, Steinle NI, Snitker S, Shuldiner AR, Mitchell BD: **A genome-wide scan of serum lipid levels in the Old Order Amish.** *Atherosclerosis* 2004, **173**(1):89-96.
73. Feitosa MF, Rice T, North KE, Kraja A, Rankinen T, Leon AS, Skinner JS, Blangero J, Bouchard C, Rao DC: **Pleiotropic QTL on chromosome 19q13 for triglycerides and adiposity: the HERITAGE Family Study.** *Atherosclerosis* 2006, **185**(2):426-432.
74. Lane RM, Farlow MR: **Lipid homeostasis and apolipoprotein E in the development and progression of Alzheimer's disease.** *J Lipid Res* 2005, **46**(5):949-968.
75. Feitosa MF, Rice T, Rankinen T, Province MA, Chagnon YC, Gagnon J, Leon AS, Skinner JS, Wilmore JH, Despres JP, et al: **Evidence of QTLs on chromosomes 13q and 14q for triglycerides before and after 20 weeks of exercise training: the HERITAGE Family Study.** *Atherosclerosis* 2005, **182**(2):349-360.
76. Klos KL, Kardias SL, Ferrell RE, Turner ST, Boerwinkle E, Sing CF: **Genome-wide linkage analysis reveals evidence of multiple regions that influence variation in plasma lipid and apolipoprotein levels associated with risk of coronary heart disease.** *Arterioscler Thromb Vasc Biol* 2001, **21**(6):971-978.
77. Machleder D, Ivandic B, Welch C, Castellani L, Reue K, Lusis AJ: **Complex genetic control of HDL levels in mice in response to an atherogenic diet. Coordinate regulation of HDL levels and bile acid metabolism.** *J Clin Invest* 1997, **99**(6):1406-1419.
78. Jacobs RL, Lingrell S, Zhao Y, Francis GA, Vance DE: **Hepatic CTP: phosphocholine cytidyltransferase-alpha is a critical predictor of plasma high density lipoprotein and very low density lipoprotein.** *J Biol Chem* 2008, **283**(4):2147-2155.
79. Willer CJ, Sanna S, Jackson AU, Scuteri A, Bonnycastle LL, Clarke R, Heath SC, Timpson NJ, Najjar SS, Stringham HM, et al: **Newly identified loci that influence lipid concentrations and risk of coronary artery disease.** *Nat Genet* 2008, **40**(2):161-169.
80. Colinayo VV, Qiao JH, Wang X, Krass KL, Schadt E, Lusis AJ, Drake TA: **Genetic loci for diet-induced atherosclerotic lesions and plasma lipids in mice.** *Mamm Genome* 2003, **14**(7):464-471.
81. Peacock JM, Arnett DK, Atwood LD, Myers RH, Coon H, Rich SS, Province MA, Heiss G: **Genome scan for quantitative trait loci linked to high-density lipoprotein cholesterol: The NHLBI Family Heart Study.** *Arterioscler Thromb Vasc Biol* 2001, **21**(11):1823-1828.
82. Yu Y, Wyszynski DF, Waterworth DM, Wilton SD, Barter PJ, Kesaniemi YA, Mahley RW, McPherson R, Waeber G, Bersot TP, et al: **Multiple QTLs influencing triglyceride and HDL and total cholesterol levels identified in families with atherogenic dyslipidemia.** *J Lipid Res* 2005, **46**(10):2202-2213.

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