

Isolation and molecular characterization of the
stearoyl-CoA desaturase (*SCD*) gene affecting
fat deposition in pigs

Dissertation

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by

Jun Ren

from Jiangxi, P.R.China

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D7

Referent: Prof. Dr. Dr. Bertram Brenig

Korreferent: Prof. Dr. Henner Simianer

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**I would like to dedicate this research
to my parents, Shixin Ren and Qiue Xu,
my wife Xueping Gao, and my son Gaofei.**

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Parts of this thesis have been published previously.

1. **Ren J**, Knorr C, Habermann FA, Fries R, Huang LS, Brenig B (2003). Assignment of the porcine stearoyl-CoA desaturase (*SCD*) gene to SSC14q27 by fluorescence *in situ* hybridization and by hybrid panel mapping. *Animal Genetics*, **34**, 471-473.
2. **Ren J**, Knorr C, Huang LS, Brenig B (2004). Isolation and molecular characterization of the porcine stearoyl-CoA desaturase (*SCD*) gene. *Gene* (accepted with revisions).
3. **Ren J**, Knorr C, Guo YM, Ding NS, Ai HS, Brenig B, Huang LS (2003). *SCD* (stearoyl-CoA desaturase) gene variants and their association with fatness traits in pigs. *Animal Genetics* (submitted).

General Introduction

Introduction

Fatness is one of economically important traits in the swine industry. Intense selection for fat production using modern statistical methods has taken place for the past fifty years (Clutter and Brascamp, 1998). At present, most swine breeding schemes aim to decreased fatness and increased lean tissue growth because of the consumer's demand for lean pork. Swine fatness traits have moderate to high heritabilities, permitting effective genetic improvement based solely on phenotypic selection. However, the use of marker-assisted selection (MAS) is expected to yield genetic gain over traditional phenotypic selection. The remarkable developments of molecular biology technologies have open new windows for investigator to identify genes or molecular markers associated with traits of economical importance in farm animals. Current strategies are involved with the chromosome or genome scan approach, the positional candidate gene approach and the direct candidate gene approach (See review by Andersson, 2001). The direct candidate gene approach is the most general and straightforward approach compared to the other two methods. Candidate genes can be identified based on the knowledge of the physiology and biochemistry of a trait. With the development of large number of molecular markers and interval-mapping method, the chromosome and total genome scan approaches have been successfully utilized to dissect quantitative trait loci (QTL) affecting economically important traits such as fatness in pigs. QTLs can be detected in a distinct chromosomal region using the experimental intercross between divergent populations, *e.g.*, European wild boar *vs* European domestic, Chinese Meishan *vs* European White. Such verified QTLs may be

exploited in MAS programs in commercial populations, and causative genes or mutations underlying the phenotypic variance may be ultimately revealed by positional candidate cloning on the basis of the verified QTLs and the comparative mapping knowledge. So far, the genome-wide significant QTLs for fatness have been consistent evidenced on the porcine chromosome 1q, 2p, 4, 6, 7, and X. Moreover, some suggestive QTLs of chromosome-wide significance affecting fatness trait were reported on the porcine chromosome 3, 5, 10 and 14. In this thesis, the recent progresses of identification of the major QTLs and the corresponding positional candidate genes for fatness traits in pigs are outlined as follow:

QTLs and positional candidate genes for fatness traits in pigs

QTLs and positional candidate genes for fatness traits on SSC 4

The first genome scan for QTLs in pigs used a European wild boar × Large White (Andersson et al., 1994) and revealed QTLs significantly affecting abdominal fat percentage, growth from birth to 70kg and length of small intestine. The QTLs were all on the porcine chromosome 4, which were confirmed by further analysis with additional markers and different statistical methods (Knott et al., 1998; Marklund et al., 1999; Knott et al., 2002). The best location of QTL was between markers *S0175* and *ATP1B1* on SSC 4. The QTL was also shown to segregate in a cross between Chinese Meishan and Large white (Walling et al., 1998; Bidanel et al., 2001; Milan et al., 2002), Iberian×Landrace intercross (Perez-Enciso et al., 2000) and Berlin Miniature×Duroc intercross (Willmers et al., 2002). The QTL locations were fairly

consistent across all tests (Table 1, Fig. 1). A joint analysis of seven different resource populations confirmed the presence of the QTLs for subcutaneous fat depth on SSC 4 in both Meishan- and wild-boar-derived populations with the location close to the marker *S0073* (Walling et al., 2000). It is both of scientific and commercial interest to know if the similar effect can be found within commercial populations. Recently, 11 QTLs for backfat and growth rate previously identified in experimental resource populations were examined for segregation in 10 different commercial populations. The QTL for fatness trait on SSC 4 was the most consistent effect across populations, this QTL was detected for fatness traits in Hampshire, Large white and Pietrain populations, indicating the QTL that explain variation between divergent populations also account for genetic variation within commercial populations (Evens et al., 2003). The finding is of particular importance from breeding point of view for the QTL can be utilized for marker-assisted selection in commercial breeding schemes. A long term goal of QTL mapping is to identify the causative genes and mutations, though it's a very difficult task. The positional candidate gene approach on the basis of comparative mapping knowledge is currently promising strategy to achieve it. Unfortunately, the QTL region is close to the break point of conserved synteny (human chromosome 1 and 8), complicating the identification of possible candidate genes. Indeed, no obvious positional candidate gene has so far been identified in the region. Although the adipocyte fatty acid-binding protein (*A-FABP*) gene was assigned to SSC 4 and supposed to control fat deposition in pigs, further studies did not support this hypothesis (Gerbens et al., 2000). Two additional candidate genes,

β -3-adrenergic receptor (*ADRB3*) and Na^+/K^+ -ATPase subunit β (*ATP1B1*) gene were within the QTL confidence interval (Knott et al., 1998). However, their effects on fatness traits remain unknown to date.

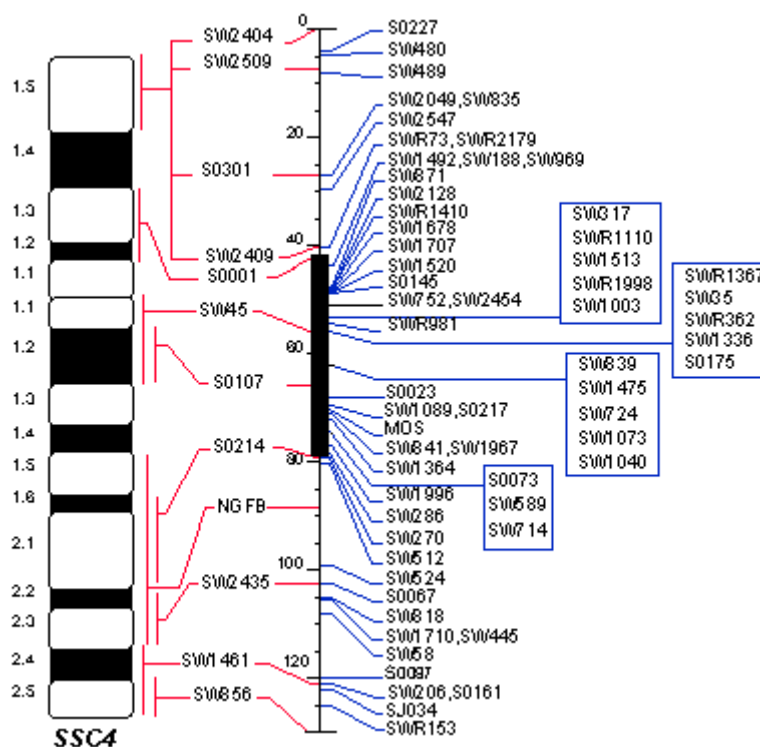


Figure 1 Genomic region for fatness traits on the porcine chromosome 4. The confidence interval of consistently evidenced QTL is indicated by black vertical bar. The map display was based on the USDA-MARC Swine Genome Map (<http://www.genome.iastate.edu/maps/marcmap.html>).

QTLs and positional candidate genes for fatness traits on SSC 7

The porcine chromosome 7 contains the swine lymphocyte antigen (SLA) complex, the major histocompatibility complex (MHC) of the *sus scrofa* species. Many studies indicated the association of the SLA polymorphisms with immunology, production and reproductive traits (see review by Chardon et al., 2000). The QTL significantly affecting fatness traits was consistently evidenced in the region surrounding the SLA region among different Meishan-derived experimental populations (Table 2, Fig. 2). In a Meishan-White Composite reciprocal backcross population, the maximum F-ratio

Table 1 QTL significantly affecting fatness traits on SSC 4 in different populations.

Populations	Institutions	QTL locations	Traits	Favorable allele	Candidates	References
Hampshire, Pietrain and Large White	PIC, UK	<i>Sw35-Sw839</i>	Fatness			Evans et al., (2003)
Meishan × Large White	INRA, France	<i>S0001-Sw1089</i>	Backfat thickness	Large White		Milan et al., (2002)
Meishan × Large White	INRA, France	<i>S0001-Sw1089</i>	Backfat thickness	Large White		Bidanel et al., (2001)
Berlin Miniature × Duroc	University of Bonn, Germany	<i>S0001-S0214</i> ; close to <i>STS_Bio1</i>	Backfat thickness eye muscle area, carcass length	Duroc		Wimmers et al., (2002)
Iberian × Landrace	SGIT-INIA Spain	<i>Sw839-S0214</i> , close to <i>Sw839</i>	Backfat thickness, Backfat weight, % linoleic acid	Landrace		Perez-Enciso et al., (2000)
Joint analysis of seven resource populations	Roslin institute, UK	Close to <i>S0073</i>	Backfat thickness			Walling et al., (2000)
Wild boar × Large White	Uppsala, Sweden	<i>S0175-ATP1B1</i> , close to <i>S0107</i>	Backfat thickness, % abdominal fat	Large white	<i>ADRB3</i> , <i>ATP1B1</i>	Knott et al., (1998)
Meishan × Large White	Roslin , UK	<i>S0175-GBA</i>	Backfat thickness	Large White		Walling (1998)

of the QTL for six backfat thickness measures was close to the location of the tumor necrosis factor alpha (*TNF α*) gene, which was located in the SLA region (Rohrer, 2000; Rohrer and Keele, 1998a). The QTL effects were also detected in Iowa State University resource families within the same region that was near *TNF α* (Wang et al., 1998). The existence of QTL influencing fatness on SSC 7 was further confirmed by analyzing other Meishan-White populations. The QTL was localized a 33-cM confidence interval (*Sw1369-S0102*) in a Meishan \times Dutch Large White and Landrace F₂ cross (Rattink et al., 2000). In the INRA QTL experiment, the most likely QTL location was supposed to be between the SLA and marker *S0102* (Milan et al., 2002). A striking characteristic of the QTL across all populations was that the obesity decreasing allele was originated from Meishan pig, irrespective of its obese phenotype. Wada et al (2000) also reported a significant QTL for back fat thickness around the SLA region on SSC 7 in a Meishan \times Goettingen Miniature cross population. Moreover, The greatest evidence for QTL for back fat was detected in an 80-cM interval around the SLA (*TNFB-S0101*) in a Berkshire \times Yorkshire resource family. Different from the Meishan cryptic allele for leanness, Berkshire alleles were associated with considerably greater fatness in that study as expected from breed differences (Malek et al., 2001). It is interesting to note that the highly selected commercial populations are recently evidenced for the presence of the QTL for fatness (Nagamine et al., 2003). The maintenance of such QTL (alleles) in commercial populations indicates its strong pleiotropic effects, presumably on fitness traits such as survival and fertility. The major QTL for fatness trait detected in experimental cross also explains the considerable phenotypic variance in commercial populations and have not yet reached fixation through the process of artificial selection, supporting its encouraging application in MAS programs in pig breeding.

The consistent findings for the QTL near the SLA region on SSC 7 indicate that this QTL is real and has generally large effects on fat deposition in pigs. Comparative mapping of the SLA region was performed using IMpRH panel to supply positional candidate genes underlying the QTL effects. The SLA is assigned in the SSC 7p12-q12 region and homologous to HSA 6p23-q12 harboring human MHC (Demeure et al., 2003). A global conservation of gene order and distance was revealed between the two MHC regions with the exception of a 3.7-Mb rearranged fragment. The Colipase (*CLPS*) and bone morphogenetic protein 5 (*BMP5*) genes within the SLA region were proposed as positional candidate genes (Demeure et al., 2003). *CLPS* prevents the inhibition of pancreatic lipase activity by surface-active agent such as bile salts by binding the enzyme to its triacylglycerol substrate. *CLPS* gene was mapped to the QTL interval between the *TNFB* and *S0102* (Brown and Archibald, 2002). *BMP5* influences the skeleton development and is required for normal development of several soft tissues (King et al., 1994). However, it should be mentioned that the SLA has a high gene density and is highly polymorphic, numerous genes might be considered as positional candidate genes in this region.

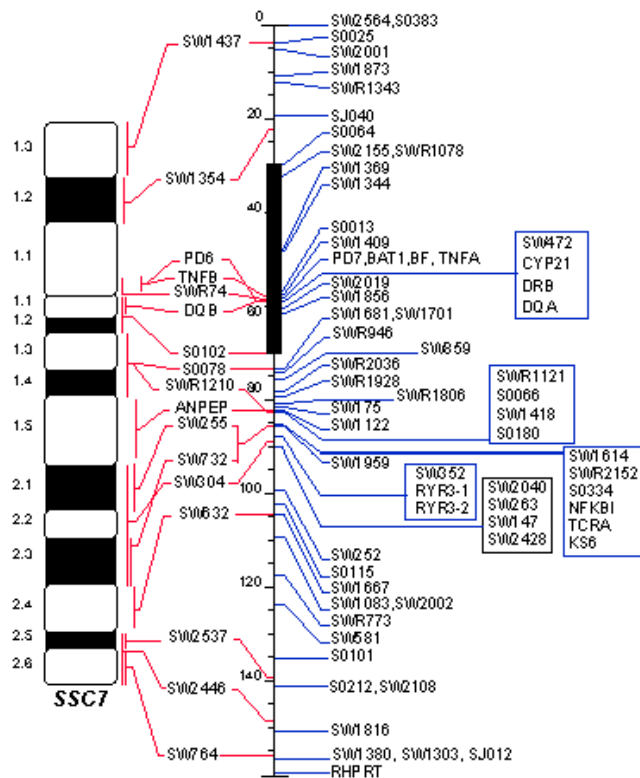


Figure 2 Genomic region for fatness traits on the porcine chromosome 7. The confidence interval of consistently evidenced QTL is indicated by black vertical bar. The map display was based on the USDA-MARC Swine Genome Map (<http://www.genome.iastate.edu/maps/marcmmap.html>).

Table 2 QTL significantly affecting fatness traits on SSC 7 in different populations.

Populations	Institutions	QTL Locations	Traits	Favorable allele	Candidates	References
5 western commercial pig populations	Roslin institute, UK	<i>TNFB-SLA</i>	Fatness	Meishan		Nagamine et al., (2003)
Meishan × Large White	INRA, France	<i>SLA-S0102</i>	All fatness traits	Meishan		Milan et al., (2002)
Meishan × Large White	INRA, France	<i>SLA-S0102</i>	BF14w, 17w, 22w BF40kg, BF60kg	Meishan	<i>BMP5</i> ; <i>CLPS</i>	Bidanel et al., (2001)
○ Berkshire × Yorkshire	Iowa State University, USA	<i>TNFB-S0101</i> (80cM)	Backfat thickness	Yorkshire		Malek et al., (2001)
Meishan × Dutch Large White or Landrace	University of Wageningen, The Netherlands	<i>Sw1369-S0102</i> (33cM)	Backfat thickness	Meishan		Rattink et al., (2000)
Meishan × Dutch Large White or Landrace	University of Wageningen, The Netherlands	<i>SLA-Sw1856</i>	Backfat thickness	Meishan		de Koning et al., (2000)
Goettingen Miniature × Meishan	NIAI, Japan	<i>Swr1078-TNFB</i> <i>Sw1369-S0102</i>	Backfat thickness			Wada et al., (2000)

Table 2 QTL significantly affecting fatness traits on SSC 7 in different populations (continued).

Resource population	Institutions	QTL Locations	Traits	Favorable allele	Candidates	References
Meishan × Dutch Large White or Landrace	Wageningen University, The Netherlands	<i>S0064-S0102-Sw175</i>	Backfat thickness	Meishan		de Koning et al., (1999)
Meishan × White reciprocal backcross	USDA, USA	5cM after SLA	Backfat thickness at 14 and 26 weeks	Meishan		Rohrer (2000)
Meishan or Minzhu × Duroc or Hampshire or Landrace	Iowa State University, USA	<i>S0064-S0102</i> , close to <i>TNFα</i>	Backfat thickness	Meishan	<i>TNFα</i> <i>CLPS</i>	Wang et al., (1998)
Meishan × White reciprocal backcross	USDA, USA	Close to <i>TNFα</i>	Backfat thickness	Meishan		Rohrer & Keele (1998a, b)
Pietrain × Large White	University of Liege, Belgium	<i>S0066-Sw252</i>	% Belly fat	Pietrain		Nezer et al., (2002)

BF14w, 17w, 22w: Average backfat thickness at 14, 17 and 22 weeks; BF40kg, BF60kg: Average backfat thickness at 40 and 60kg live weight; % Belly fat= belly weight/carcass weight.

QTLs and positional candidate genes for fatness traits on SSC 2p

A whole genome scan using a Pietrain \times Large White intercross initially revealed a parentally imprinted QTL with major effects on fat deposition and muscle mass at the centromeric end of chromosome 2 (Nezer et al., 1999; Fig. 3). The result was confirmed at the same location in the same population with additional markers and production traits. The imprinted QTL was evidenced for three fatness traits (backfat thickness, % back fat and % fat cut) and three muscularity traits (% loin, % ham and % lean cut) (Nezer et al., 2002). Meanwhile, this QTL was shown to segregate in a European wild boar \times Large White intercross and explained 10-20% of the variation in backfat thickness and 15-30% of the phenotypic variation in muscle mass (Jeon et al., 1999). For the distal end of p arm of SSC 2, the homologous human region is HAS 11p, encompassing several imprinting genes including the parentally imprinting insulin-like growth factor 2 (*IGF2*) gene. Hence, the *IGF2* locus was considered as a strong positional candidate gene in the region (Nezer et al., 1999). However, initial screening of polymorphisms in the coding and regulatory regions of the *IGF2* gene failed to find any causative mutations. To uncover causative mutations underlying the QTL, a haplotype sharing approach was used to refine the QTL location. The QTL was narrowed in an ~250-kb interval between the markers *370SNP6/15* and *SWC9*, which contains *IGF2* and insulin (*INS*) gene as the only known paternally expressed genes (Nezer et al., 2003). Further analysis provided convincing evidences that a G /A transition in intron 3 of *IGF2* (at position 3072 nucleotide) is the causative mutation explaining the effects of the QTL. The wild type (G) binds a nuclear factor, probably a

repressor and this interaction is abrogated by the mutation (A), resulting in an increase in *IGF2* mRNA expression in postnatal muscle and consequently higher muscle mass and lower fat deposition (Van Laere et al., 2003). This extraordinary finding indicates that regulatory mutations in the non-coding intronic region are also important for controlling phenotypic variation besides the polymorphisms in the coding and flanking regulatory regions.

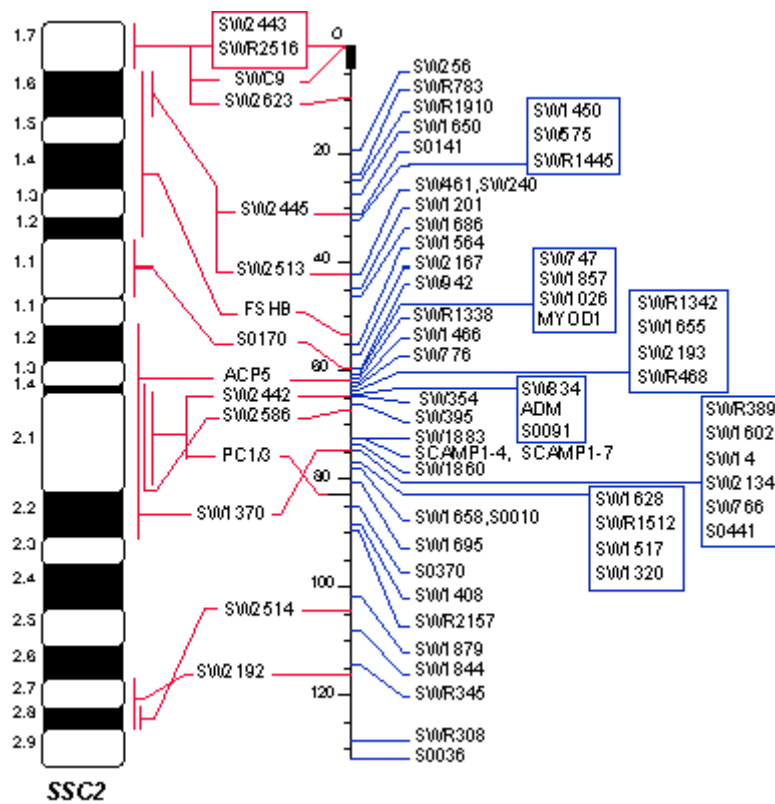


Figure 3 Genomic region for fatness traits on the porcine chromosome 2p. The confidence interval of consistently evidenced QTL is indicated by black vertical bar. The map display was based on the USDA-MARC Swine Genome Map (<http://www.genome.iastate.edu/maps/marcmap.html>).

It should be noted that a different paternally expressed QTL for back fat thickness was found at 35 cM from the *IGF2* region in an experimental cross between Meishan pigs and commercial Dutch pigs (de Koning et al., 2000; Rattink et al., 2000). So far, no promising positional candidate gene has been proposed, partially due to the fact

that the QTL region is crossing the breakpoint of two conserved synteny group, HSA 11 and HSA 19. The extremity of SSC 2p was also evidenced for one QTL affecting both lean and, to a lesser extent, fat tissue weights in the INRA Meishan × Large White F₂ populations. The position was quite similar to the *IGF2* region. However, the QTL did not exhibit any significant imprinting effect (Milan et al., 2002), supporting the finding that the *IGF2* causative mutation was just present in some founders of different experimental resource populations (Van Laere et al., 2003).

QTLs and positional candidate genes for fatness traits on SSC 1q

A genome-wide significance was evidenced for fatness and growth traits in the telomeric region of the SSC 1q in several studies involved Meishan × White pig intercross populations and Meishan synthetic lines (Fig. 4). This region was shown to influence backfat depth, loin eye area and trimmed wholesale product weight in the USDA resource families, the Meishan allele tended to increase the backfat depth (Rohrer, 2000; Rohrer and Keele, 1998a, b). The genomic area was also identified as affecting backfat thickness in a cross between Meishan and Dutch Large White and Landrace lines (de Koning et al., 1999). Moreover, strong evidences for QTL were found for lean and fat cut weight, backfat thickness and postweaning growth rate at the same region, *i.e.* the end of SSC 1q and close to the *Sw1301* markers in the INRA Meishan × Large White experimental population (Milan et al., 2002; Bidanel et al., 2001). These results were in good agreement with the recent finding that the QTL effects were confirmed in a Meishan synthetic line (Evens et al., 2003). In this QTL

region, the steroidogenic factor 1(*SFI*) and LIM homeodomain transcription factor (*Lhx3*) gene were identified and considered candidate genes for this QTL due to their position and physiological role (Smith et al., 2001).

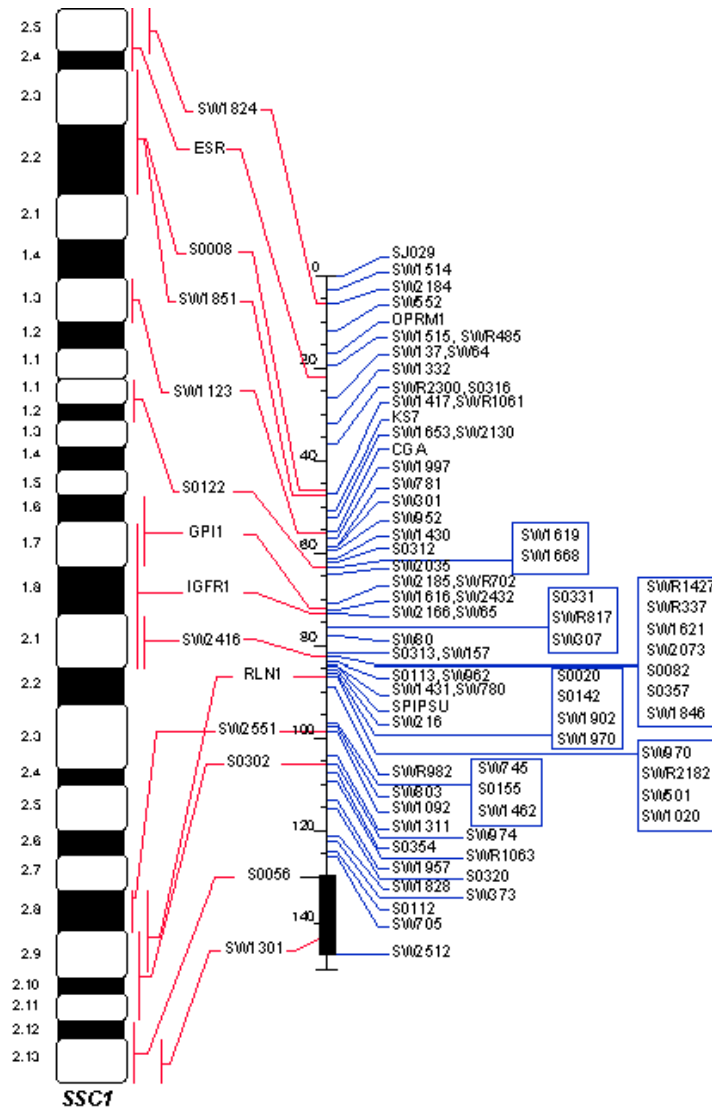


Figure 4 Genomic region for fatness traits on the porcine chromosome 1q. The confidence interval of consistently evidenced QTL is indicated by black vertical bar. The map display was based on the USDA-MARC Swine Genome Map (<http://www.genome.iastate.edu/maps/marcmap.html>).

QTLs and positional candidate genes for fatness traits on SSC 6

A QTL for backfat thickness and intramuscular fat (IMF) content was identified on

the porcine chromosome 6 in a F₂ cross between Iberian × Landrace pigs. The most likely position of the QTL is in the interval between the markers *S0228* and *Sw1881* and the maximum *F*-ratio is close to *Sw1881* (Óvilo et al., 2000; Fig. 5). So far this genome-wide significant QTL has not been detected in other Meishan or European wild boar derived resource populations, indicating that the Iberian genetic background is partially different from that of Meishan and European wild boar. Two positional candidate genes within the QTL region, *i.e.* the heart fatty acid-binding protein (*H-FABP*) and the leptin receptor (*LEPR*) gene were utilized for fine mapping of the QTL region in combination of seven microsatellite markers using the same experimental population. The QTL effects on fatness and IMF were confirmed and mapped in the same marker bracket (Óvilo et al., 2002). The H-FABP protein is involved in the intracellular transport of fatty acids in skeletal muscle and plays an important role in lipid metabolism. A *Hae*III restriction fragment length polymorphism (RFLP) in the intron 2 of the *H-FABP* was initially indicated to be associated with fatness traits in the Duroc breed (Gerbens et al., 1999). However, more recent works have described this association with only IMF (Gerbens et al., 2000). In the Iberian × Landrace F₂ population, the *H-FABP* polymorphism showed significant effects on IMF and eye muscle area in an animal model (Óvilo et al., 2002). Due to its interaction with leptin, the *LEPR* gene is related to the control of feed intake and the regulation of energy balance in mammals (Ruiz-Cortes et al., 2000). A *Hpa*II-RFLP in the fourth intron of the *LEPR* gene showed significant effects on backfat thickness and IMF in the Iberian × Landrace F₂ population in an animal model

(Óvilo et al., 2002). However, when the candidate gene effect was included in a QTL regression analysis, both the *H-FABP* and *LEPR* associations were not observed, suggesting that they must not be the causative mutations for the QTL but only markers in linkage disequilibrium with them (Óvilo et al., 2002). Hence, Polymorphisms in other positional candidate genes or new polymorphisms in the coding and regulatory regions of the *H-FABP* and *LEPB* genes are required to identify the causative mutations underlying the QTL effects on SSC 6.

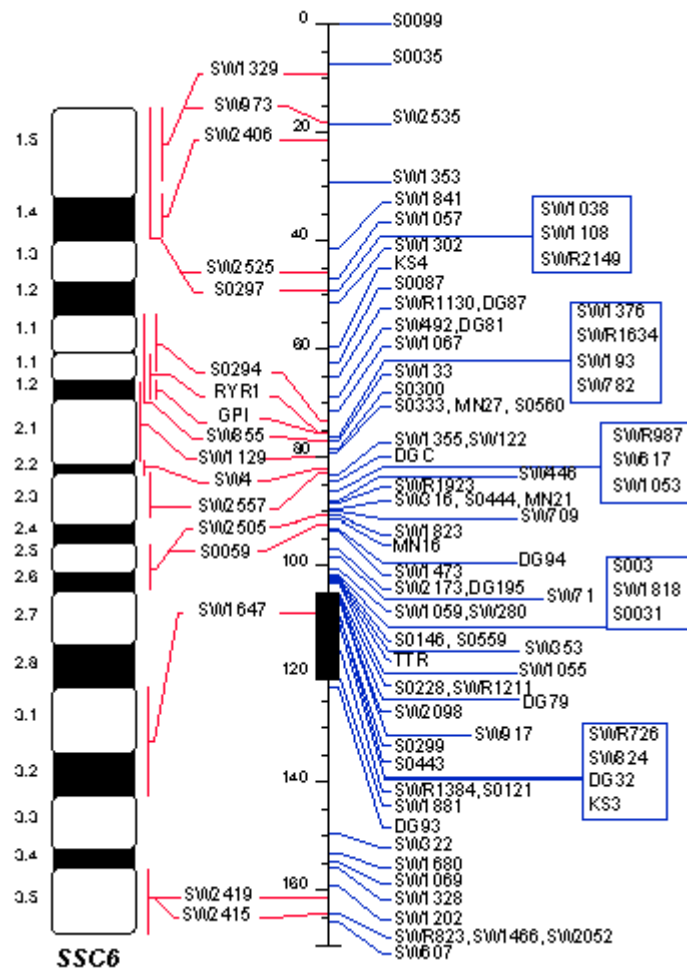


Figure 5 Genomic region for fatness traits on the porcine chromosome 6. The confidence interval of the QTL is indicated by black vertical bar. The map display was based on the USDA-MARC Swine Genome Map (<http://www.genome.iastate.edu/maps/marcmap.html>).

QTLs and positional candidate genes for fatness traits on SSC X

Several studies reported the presence of a QTL for fatness traits on the porcine chromosome X (Fig. 6). Significant QTL was detected on SSC X in the USDA resource population, which significantly affected backfat thickness and leanness traits including loin area and trimmed wholesale product weight (Rohrer and Keele, 1998a, b). This genomic region (in the interval between the markers *Sw2456* and *Sw2476*) was also evidenced for the existence of a QTL affecting backfat thickness in a Meishan × Dutch White pigs intercross (Harlizius et al., 2000). In the INRA QTL experiment, a significant QTL was identified for backfat, ham and loin weight in the similar region (near the marker *Sw1994* on SSC X), with favourable effects of Large White alleles. The QTL effects explain 36 and 41% of phenotypic variance of loin and backfat weight, respectively (Milan et al., 2002). These consistent findings support the reliability of the QTL in this region. Two candidate genes, the androgen receptor (*AR*) and the phosphoglycerate kinase 1 (*PGK1*) were located within the QTL region on the basis of comparative mapping (Harlizius et al., 2000). However, their associations with fatness traits in pigs remain to be seen to date.

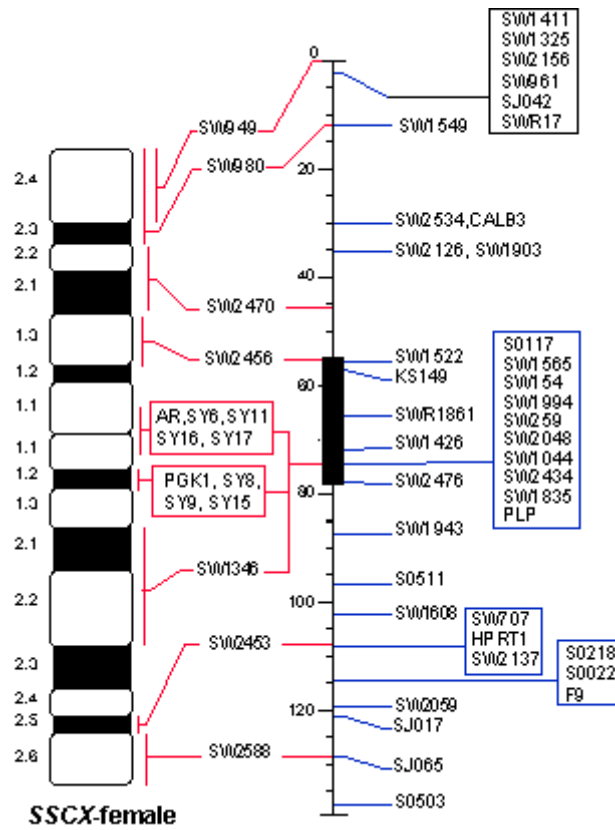


Figure 6 Genomic region for fatness traits on the porcine chromosome X. The confidence interval of consistently evidenced QTL is indicated by black vertical bar. The map display was based on the USDA-MARC Swine Genome Map (<http://www.genome.iastate.edu/maps/marcmmap.html>).

SCD: the candidate gene for fatness traits in pigs

The discovery of leptin gene

In 1994, Friedman and his colleagues identified an obesity-decreasing gene designated by *leptin* by tracing the genes in a mutant strain of extremely obese mice (Zhang et al., 1994). It was the identification of *leptin* gene that opens the door to the obesity research in mammals. Leptin is a 16-kDa protein secreted from white adipocyte. It has been implicated in the regulation of feed intake, energy expenditure, whole-body energy balance and neuroendocrine axis in mammals (Campfield et al., 1995). The leptin-deficient mice (*ob/ob*) are extremely obese, and administration of leptin protein into *ob/ob* mice resulted in reduced feed intake, weight loss and improved reproduction (Zhang et al., 1994). Leptin is believed to produce weight loss by decreasing the animals' appetite while at the same time revving up their metabolic rate. Plasma leptin has been demonstrated to infuse into the arcuate nucleus in the hypothalamus and inhibit the neuropeptide Y (NPY) and agouti-related peptide (AgRP), causing the reduced appetite and metabolism. Meanwhile, Leptin stimulates the POMC/CART neurons and activates the release of α -melanocyte-stimulating hormone (MSH), consequently inhibiting eating (Marx, 2003).

Because of its physiological properties in the energy metabolism, the *leptin* gene has been considered as a strong candidate gene controlling obesity in livestock. Plasma leptin levels in cattle and sheep increase linearly with increased body fat mass and with increased energy balance (Delavaud et al., 2000; Ehrhardt et al., 2000). A cytosine (C) to thymine (T) missense mutation was identified in exon 2 of the bovine

leptin gene, and the T allele appeared to be associated with fatter carcasses and higher leptin mRNA level (Buchanan et al., 2002). In swine, the *leptin* gene is exclusively expressed in adipose tissue, and leptin mRNA level in sera was reported to be greater in adipose tissue from obese pigs than lean pig (McNeel et al., 2000). The porcine *leptin* gene consists of three exons, and a 504-bp open reading frame encodes a peptide of 167 amino acids (Bidwell et al., 1997). Seven non-invasive single nucleotide polymorphisms (SNPs) were characterized in the porcine *leptin* gene. Kennes et al (2001) presented a possible association between the A2845T and T3469C SNPs with feed intake and growth rate traits in Landrace pigs. The T3469C polymorphism was also suggested to affect fatness in pigs (Jiang and Gibson, 1999). Nevertheless, those evidences are not conclusive, for those mutations do not alter the encoding protein structure and so far none of interval confidence of major QTL for fatness in pigs harbors the *leptin* gene. Linkage disequilibrium with another causative mutations was proposed to be more likely explanation of the association (Jiang and Gibson, 1999). In human, several studies indicated the polymorphisms in the *leptin* gene were not the primary cause of obesity (Carlsson et al., 1997), though some rare case of human obesity caused by leptin deficiencies were treatable by the hormone. For this reason, numerous studies have been focused on the biochemical pathways through which leptin works to uncover other obesity regulators since the discovery of *leptin* gene.

SCD gene is a key component in the leptin-signaling pathway

To pinpoint the most important leptin-regulated gene, DNA microarrays were used to

compare the transcription profiles between the leptin-treated *ob/ob* mice and the food restriction group. Stearoyl-CoA desaturase-1 (*SCD-1*) gene was most prominent in six clusters of genes specifically regulated by leptin (Cohen et al., 2002). Leptin was found to specifically repress RNA level and enzymatic activity of *SCD-1* gene. *SCD-1* RNA levels were highly elevated in *ob/ob* mice liver, whereas normalized at 2 days after treated by leptin. To elucidate whether *SCD-1* mediate the leptin's metabolic effects, Cohen et al. (2002) intercrossed the leptin-deficient *ob/ob* mice and the *ab^J/ab^J* mice with naturally occurring mutations in *SCD-1*. It was notable that double-mutant *ab^J/ab^J; ob/ob* mice were significantly less obese than *ob/ob* controls and had markedly increased energy expenditure. The *ob/ob* mice were characterized for massively enlarged livers that were engorged with lipid, and had high levels of liver triglyceride and very low density lipoprotein (VLDL). However, the *ob/ob* mice with mutations in *SCD-1* had normal livers with significantly reduced triglyceride storage and VLDL production. These data suggest that SCD-1 is an important biological modulator of lipid metabolism and indicate that SCD-1 is required for the fully developed obese phenotype of *ob/ob* mice, and down-regulation of SCD-1 is an important component of leptin's metabolic actions.

The role of SCD gene in lipid metabolism

Stearoyl-CoA desaturase is a key enzyme in the cellular biosynthesis of monounsaturated fatty acids. It is located in the endoplasmic reticulum membrane and catalyzes the insertion of a double bond between carbon atoms 9 and 10 in a spectrum of saturated fatty acids. The preferred substrates are stearoyl-CoA (C18:0) and

palmitoyl-CoA (C16:0), which are converted to oleic acids (C18:1) and palmitoleic acids (C16:1) by SCD enzyme, respectively (Enoch et al., 1976). The oxidative reaction is catalyzed by a set of microsomal electron-transport proteins composed sequentially of NADH cytochrome b5 reductase, cytochrome b5 and the terminal SCD (Fig. 7). Stearoyl-CoA desaturase is the rate-limiting component in this reaction.

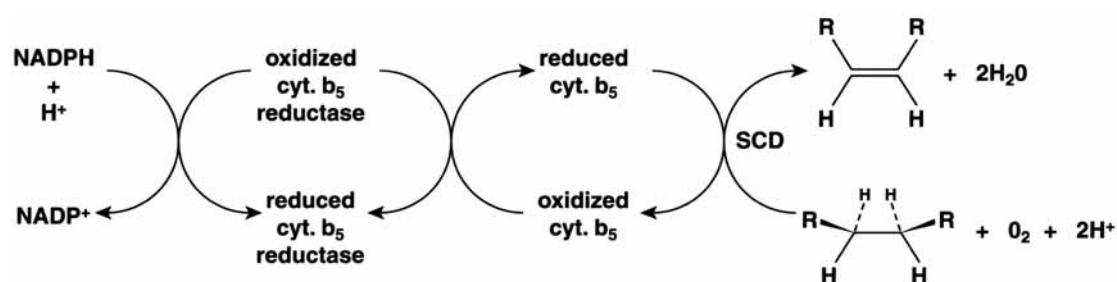


Figure 7 The pathway of electron transfer in the desaturation of fatty acids by SCD.

It has been shown that a deficiency of SCD-1 ameliorates the obesity of *ob/ob* mice and completely corrects the hypometabolic phenotype of leptin deficiency (Cohen et al., 2002). The *SCD-1* deficient mice (*SCD1*^{-/-}) were also found to reduce body adiposity despite the increased feed intake, increase insulin sensitivity and be resistant to diet-induced weight gain (Ntambi et al., 2002). Furthermore, Stearoyl-CoA desaturase has been implicated as a nutritional target for lipid lowering; the beneficial effects of dietary (n-3) fatty acids for lowering serum lipids in rodents are due in part to decreased expression of *SCD* gene (Kramer et al., 2003). These observations suggest that *SCD* gene is a central lipogenic enzyme, playing an essential role in the lipid metabolism. Several explanations have been postulated for the molecular basis of the lipid-lowering effects of *SCD* deficiency, through it is not yet fully understood.

The revving up fatty acid oxidation may account for the decreasing body fat caused

by *SCD* deficiency. The deletion of *SCD-1* gene was reported to up-regulate the lipid oxidation enzymes such as acyl-CoA oxidase, very long chain acyl-CoA dehydrogenase and carnitine palmitoyltransferase-1 (*CPT-1*) gene in mice (Ntambi et al., 2002). All these genes are targets of peroxisome proliferators-activated receptor α (*PPAR* α) and contain *PPAR* α response region in their promoters. Changes in *SCD-1* activity presumably alter the levels of ligand for *PPAR* α , resulting in an increased expression of *PPAR* α and consequently an increased expression of *PPAR* α -targeted lipid oxidation enzymes. Moreover, if *SCD-1* gene is blocked, the intercellular levels of saturated fatty acyl-CoAs will build up and inhibit acetyl-CoA carboxylase (*ACC*) through a well-known feedback mechanism, reducing cellular levels of malonyl CoA. Malonyl CoA is a key control point of the lipid β -oxidation. It inhibits *CPT-1* gene controlling the import and oxidation of fatty acids in mitochondria. Hence, the reduced levels of malonyl CoA will stimulate fatty acids import to mitochondria, resulting in an increased lipid oxidation (Ntambi et al., 2002).

An impaired triglyceride and cholesterol biosynthesis could partially underlie the adiposity-loss effects of *SCD* deficiency. The oleic and palmitoleic fatty acids, the products of *SCD* enzyme, are main components of triglyceride and cholesterol, which are required for hepatic lipid storage and VLDL synthesis. It had been reported that the *SCD-1* deficient mice had very low levels of triglycerides in the VLDL and low density lipoprotein fractions compared with normal animals (Miyazaki et al., 2000). A lipogenic diet failed to induce triglyceride synthesis in the *SCD-1* deficient mice, despite the incorporation of oleate into the liver. Only endogenous monounsaturated

fatty acids produced by *SCD-1* gene are required for triglyceride synthesis in mice liver (Miyazaki et al., 2001). Meanwhile, the deletion of *SCD-1* gene was shown to down-regulate sterol regulator element binding protein-1 (*SREBP-1*) gene and its targeted lipogenic genes such as fatty acids synthase (*FAS*) and glycerol phosphate acyl-CoA transferase (*GPAT*) gene, thereby reducing triglyceride synthesis and storage (Ntambi et al., 2002). These data indicate that *SCD-1* gene expression is a key control point in the induction of triglyceride synthesis in liver.

Alternative mechanisms may also explain the adiposity-loss effects of *SCD* deficiency. It is well established that the ratio of saturated to unsaturated fatty acids incorporated into phospholipids determines the membrane fluidity. Hence, Changes in *SCD* activity could alter the membrane fluidity by altering the ratio of saturated to unsaturated fatty acids, which could affect signal transduction. It should be mentioned that alterations of this ratio have been implicated in various disease state including hypertension, neurological diseases, immune disorders and cancer in addition to adiposity (see review by Ntambi, 1999).

In summary, stearoyl-CoA desaturase is a rate-limiting enzyme in the biosynthesis of monounsaturated fatty acids. It plays a crucial role in regulating the body weight and adiposity in the complex leptin-signaling pathway, spurring *SCD* gene as a strong candidate gene for obesity in mammals.

Characterization of SCD genes in mammals

SCD genes have been so far characterized in several mammals including mouse, rat (Mihara, 1990), human (Zhang et al., 1999), goat (Bernard et al., 2001) and sheep

(Ward et al., 1998). The murine *SCD* gene was first isolated and cloned by Ntambi and his colleagues in 1988 (Ntambi et al., 1988). Since then, three additional murine *SCD* genes have been characterized. Their encoding regions and predicted proteins are highly homologous, whereas their expression profiles differ remarkably. *SCD1* is mainly expressed in adipose tissues and liver (Ntambi et al., 1988), *SCD2* is principally expressed in brain (Kaestner et al., 1989), *SCD3* is skin-specifically expressed (Zheng et al., 2001), whereas *SCD4* is exclusively expressed in the heart (Miyazaki et al., 2003). The reasons for having four *SCD* gene isoforms in mice remain to be seen. In human, one functional *SCD* gene was identified on chromosome 10, which generated two alternative transcripts of 3.9 and 5.2 kb. An inactive, fully processed pseudogene was located on human chromosome 17 (Zhang et al., 1999). In sheep and goat, *SCD* mRNA is transcribed from a single gene, which was assigned to ovine chromosome 22q21 (Bernard et al., 2001; Ward et al., 1998). So far, only a 1,003-bp porcine *SCD* mRNA sequence was deposited in the database (GenBank accession no. Z97186). The sequence was incomplete, especially lacking the start and stop codon. The aim of this study is to isolate and characterize the complete porcine *SCD* gene, and to elucidate its association with fatness traits in pigs. The chromosomal assignment, the genomic organization, the complete cDNA and genomic DNA sequence of the porcine *SCD* gene, the expression profiles in different tissues, the gene polymorphisms among different pig breeds and their association with fatness traits in a White Duroc × Chinese Erhualian F₂ population were described in this thesis.

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2

Assignment of the porcine stearoyl-CoA desaturase (*SCD*) gene to SSC14q27 by fluorescence *in situ* hybridization and by hybrid panel mapping

(Published in *Animal Genetics*)

Isolation and molecular characterization of the porcine stearoyl-CoA desaturase (*SCD*) gene

(Accepted by *GENE* with revisions)

4

SCD (stearoyl-CoA desaturase) gene variants and their association with fatness traits in pigs

(Submitted to *Animal Genetics*)

Summary

Stearoyl-CoA desaturase (*SCD*) is a rate-limiting enzyme in the biosynthesis of unsaturated fatty acids. So far the porcine *SCD* gene has not been characterized. The isolation and molecular characterization of the full-length cDNA and genomic DNA sequence of the porcine *SCD* gene were described in the thesis. The 5134 bp cDNA contains a 1080 bp open reading frame encoding a protein of 359 amino acids with a calculated molecular mass of 41.3 kDa and theoretical isoelectric point of 9.4. The porcine *SCD* shares high identity (>80%) with the other mammalian *SCD*. To further elucidate the genomic structure of the porcine *SCD* gene, 20,985 bp of genomic DNA sequence was determined encompassing the complete porcine *SCD* gene. Similar to the other mammalian orthologs, particularly in term of exon size and exon/intron boundary, the porcine *SCD* gene spans a transcription unit of 16,186 bp, consisting of six exons with sizes ranging from 131 bp to 4048 bp, and five introns varying in size from 518 bp to 4784 bp. The unusual long 3' UTR of 3848 bp as opposed to the 176 bp 5' UTR appears in the last exon. A comparative analysis of different mammalian *SCD* promoters identified some regulatory domains required for the transcription regulation in the 5' flanking sequence of the porcine *SCD* gene, such as the conserved polyunsaturated fatty acid response region (PUFA-RE). Reverse transcription (RT)-PCR result indicates that the *SCD* gene is expressed ubiquitously in pigs. The porcine *SCD* gene was assigned to chromosome 14q27 by fluorescence in situ hybridization (FISH) and screening of hybrid panels with intronic primers. A total of 26 gene polymorphisms were revealed in the 21 kb DNA sequence, including 24

single nucleotide polymorphisms (SNPs), a 24 bp length polymorphism in the fourth intron and a triplet nucleotide insertion in the fifth intron. None of SNPs lead to an amino acid exchange. Significant differences in allele frequencies of the SNP T(-233)C and the SNP C(641)T (number refer to the corresponding position starting with +1 at the adenine of initiation codon ATG) were observed in samples of three Western commercial pig breeds (Landrace, Large White, and Duroc) and three Chinese indigenous pig breeds (Erhualian, Luchuan, and Huai). The Western pig breeds revealed higher frequencies of the allele *T* at the SNP T(-233)C, whereas the Chinese pig breeds showed higher frequencies of the allele *T* at the SNP C(641)T. Associations of SNPs T(-233)C and C(641)T with fatness traits have been investigated in F_2 animals of a White Duroc \times Erhualian pig resource family and a purebred White Duroc population. Significant associations were observed between the SNP C(641)T and backfat thickness at the 6-7th rib, backfat thickness at the last rib, and the average backfat thickness at four points (at the shoulder, the 6-7th rib, the last rib and the hip joint) in the F_2 resource family ($P < 0.05$). The allele *T* has an unfavorable effect (*i.e.* positive) on backfat thickness.

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The Porcine *SCD* mRNA and DNA sequence

LOCUS AY487829 5134 bp mRNA linear MAM 07-JAN-2004
DEFINITION Sus scrofa stearyl-CoA desaturase (SCD) mRNA, complete cds.
ACCESSION AY487829
VERSION AY487829.1 GI:40549307
KEYWORDS .
SOURCE Sus scrofa (pig)
ORGANISM [Sus scrofa](#)
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
Mammalia; Eutheria; Cetartiodactyla; Suina; Suidae; Sus.
REFERENCE 1 (bases 1 to 5134)
AUTHORS Ren,J., Knorr,C., Huang,L. and Brenig,B.
TITLE Isolation and molecular characterization of the porcine
stearyl-CoA desaturase (SCD) gene
JOURNAL Unpublished
REFERENCE 2 (bases 1 to 5134)
AUTHORS Ren,J., Knorr,C. and Brenig,B.
TITLE Direct Submission
JOURNAL Submitted (26-NOV-2003) Institute of Veterinary Medicine,
Georg-August-University of Goettingen, Groner Landstr.2, Goettingen
37073, Germany
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 Mammalia; Eutheria; Cetartiodactyla; Suina; Suidae; Sus.
 REFERENCE 1 (bases 1 to 20985)
 AUTHORS Ren,J., Knorr,C., Huang,L. and Brenig,B.
 TITLE Isolation and molecular characterization of the porcine
 stearyl-CoA desaturase (SCD) gene
 JOURNAL Unpublished
 REFERENCE 2 (bases 1 to 20985)
 AUTHORS Ren,J., Knorr,C. and Brenig,B.
 TITLE Direct Submission
 JOURNAL Submitted (26-NOV-2003) Institute of Veterinary Medicine,
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 37073, Germany
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20941 cccgggcct gccagcctg ctgcaacca ggccacagag agctc

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1. Yan XM, **Ren J**, Guo YM, Ding NS, Chen KF, Gao J, Ai HS, Chen CY, Ma JW, Huang LS (2003). Research on the genetic variations of α 1-fucosyltransferase (*FUT1*) gene in 26 pig breeds. *Yi Chuan Xue Bao*, **30**, 830-834 (PMID: 14577374).
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10. Lin WH, Huang LS, **Ren J**, Deng SH, Wang WJ, Liu BS, Zhou LH, Chen CY (2002). Research on genetic variation of heart fatty acid-binding protein gene in ten pig breeds. *Yi Chuan Xue Bao*, 29, 12-15 (PMID: 11838368, Article in Chinese).

Curriculum vitae

Ren (family name) **Jun** (surname)

Institute of Veterinary Medicine

Georg-August-University of Göttingen

Groner Landstrasse 2, 37073

Göttingen, Germany

Tel: +49-551-393318

Fax: +49-551-393392

E-mail: rjun@gwdg.de

Personal Data

Date of birth: September 6, 1974

Place of birth: Jiangxi, P.R.China

Sex: Male

Marital Status: Married

Nationality: Chinese

Education

June 2002—

Institute of Veterinary Medicine, University of Göttingen

Postgraduate student for Philosophy Doctor degree

Major: Molecular Biology of Livestock

September 1998—May 2002

Faculty of Animal Science and Veterinary, JXAU

Lecturer in Animal Genetics and Breeding

September 1995—July 1998

Faculty of Animal Science and Veterinary, JXAU

Postgraduate student for Master of Science degree

Major: Animal Genetics and Breeding

September 1991—July 1995

Department of Animal Husbandry and Veterinary

Jiangxi Agricultural University (JXAU)

Undergraduate student for Bachelor of Science degree

Major: Animal Husbandry