Mapping, Tissue Distribution and Polymorphism Study of the Porcine SOCS2 and SOCS3 Genes

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ABSTRACT : Using the somatic cell hybrid panel (SCHP) and radiation hybrid (IMpRH) panel, porcine SOCS2 gene was mapped at SSC5 (1/2) q21-q24 and closely linked with SW1383 marker (47 cR in distance), while SOCS3 gene was assigned to SSC12p11-(2/3p13) and closely linked with SW2490 (43 cR). The reverse transcriptase-polymerase chain reaction (RT-PCR) was performed to detect the expression of these two genes in the different tissues and the results showed that both SOCS2 and SOCS3 genes were widely expressed in tissues investigated (heart, liver, spleen, lung, kidney skeletal muscle, fat and brain), although some tissues showed lower gene expression. Moreover, SOCS2 and SOCS3 genes had different expression levels at different stages, in different tissues and in different breeds. A G/A substitution, which can be recognized by restriction enzyme of *Cfr421*, was observed in 5' untranslated region (5'-UTR) of SOCS2 gene. The allele frequencies was investigated by PCR-restriction fragment length polymorphism (PCR-RFLP) method and it showed that the allele frequency among Dahuabai, Erhualian, Yushan, Qingping, Large white and Landrace tested were different. Association analysis in a cross experimental populations revealed no significant association between the SOCS2 gene polymorphism and the economic traits investigated. The full-length coding regions (CDs) of porcine SOCS3 gene was obtained by RT-PCR. ***(Asian-Aust. J. Anim. Sci. 2006. Vol 19, No. 2 : 165-170)***

Key Words : Gene Mapping, Tissue Distribution, SNPs, SOCS2, SOCS3

INTRODUCTION

SOCS (suppressor of cytokine signaling) family is a kind of factors that play key roles in the negative regulation of cytokine signal transduction. They inhibit the cytokine-activated Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway through a negative feedback loop. The family currently comprises eight members: SOCS1-SOCS7 and CIS genes (Masuhara et al., 1997; Starr et al., 1997; Hilton et al., 1998). Proteins coded by this family have a similar domain structure, which consist of an N-terminal variable region, a central conserved SH2 domain, and a conserved C-terminal domain containing a SOCS box. It was reported that SOCS2 gene directly induced by GH while not by IGF-1 (Greenhalgh et al., 2002). Moreover, SOCS2 gene can bind to GH receptor and IGF-1 receptor and inhibit the binding of STAT, which might be the mechanism of SOCS2 gene inhibit GH and IGF-1 signaling pathway (Dey et al., 1998; Greenhalgh et al., 2002). SOCS2 gene deficient mice at twelve weeks after birth exhibited a 30-40% increase in body weight compared with wild-type littermates (Metcalf et al., 2000). SOCS3 gene deficient mice died in uterus due to placental defects, which suggested that SOCS3 gene might play a key role in the formation of the placenta (Roberts et al., 2001). Recent study found that SOCS3 gene was associated with inflammation reactions. SOCS3 gene negatively regulated signaling pathway of IL-6 (Lehmann et al., 2003; Yasukawa et al., 2003). In order to study the functions of porcine SOCS2 and SOCS3 genes and find some traits associated SNPs, we physically mapped porcine SOCS2 and SOCS3 genes, analyzed tissues expression distribution of these two genes at different stages and at different breeds, found a novel SNP in the 5'-UTR of porcine SOCS2 gene. Traits association analysis revealed no significant association between this SNP and the economic traits studied. Moreover, we have isolated porcine SOCS3 gene full-length CDs.

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MATERIALS AND METHODS

Primer design

All the primers employed for porcine SOCS2 and SOCS3 genes study were designed using software Primer 5.0. Primers of Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were synthesized according to the reported sequence (Janzen et al., 2000) (Table 1). All the PCR fragments were sequenced by a commercial service.

Somatic cell hybrid and radiation hybrid mapping

The somatic cell hybrid panel (SCHP) was used for chromosomal assignments and the radiation hybrid (IMpRH) panel was used for more precise mapping (Yerle et al., 1996; 1998). PCR reaction was performed in a 10 μl reaction mixture containing 25 ng of cell hybrid line DNA, 1×PCR buffer (TaKaRa), 0.3 μM of each primer (P1L, P1R and P1'L, P1'R), 300 μM of each dNTPs, 1.5 mM $MgCl_2$

Table 1. Primer pairs for Porcine SOCS2, SOCS3 and GAPDH genes fragments isolation

Primer purpose	Gene	Primer name	Primer sequence (5'-3')	Size bp	TM (°C)
Mapping	SOCS2	P1L	CTCTTTGTTGTTGTCGTTGTTG	1,018	58.5
		P1R	AGCCTTTCCTTGGGACATT		
	SOCS3	P1'L	GGCACACAAGAAGCCACACACTC	491	64
		P1'R	AGAGTGATTGAGGCAGATTGTA		
Expression	SOCS2	P2L	GATTAGAGATAGTTCGCACTCAGAC	658	65
Distribution		P2R	AGCCTTTCCTTGGGACATT		
	SOCS3	P2'L	GCGACACTTCTTCACGCTCAGC	444	69
		P2'R	TGGTCCAGGAACTCCCGAATG		
Polymorphism	SOCS2	P3L	GGGTTCTCACTGACTTCTAAGGACG	349	65
		P3R	GACGGCAATCTACTGCTTCTC		
Gene isolation	SOCS3	P4L	CTCCGTGCGCCATGGTCA	1,004	69
		P4R	GTGGAGGAAGCGGAGAGGAGA		
		P4'L	GGCGTGAGAGTCCTGTAGC	1,343	59
		P4'R	AGAGTGATTGAGGCAGATTGTA		
Internal control	GAPDH	P5L	CCTTCATTGACCTCCACTAC	320	60
		P5R	GTTGTCATACTTCTCATGGTTC		

and 1 U Taq DNA polymerase (TaKaRa). PCR profiles were 5 min at 94°C followed by 37 cycles of 40 s at 94°C, 40 s at TM (58.5°C for SOCS2 and 64°C for SOCS3), 40 s at 72°C, and a final extension of 5 min at 72°C. The PCR products were scored on 1.5% agarose gels stained with 0.5 μg/ml ethidium bromides. The SCHP and IMpRH PCR results were analyzed using the tools available on the WWW INRA server (http://www.toulouse.inra.fr/lgc/pig/hybrid.htm) (Chevalet et al., 1997) and (http://IMpRH.toulouse.inra.fr/) (Milan et al., 2000) respectively.

Tissue distribution of porcine SOCS2 and SOCS3 genes

Gene expression patterns were determined by RT-PCR. Total RNAs were extracted from 90-day embryo of Tongcheng pig, adult Tongcheng pig and adult Landrace. Eight tissues, heart, liver, spleen, lung, kidney, skeletal muscle, fat and brain, were selected to study the expression patterns. All RNAs were isolated using TRIzol reagent (Invitrogen), treated with RNAse-free DNase I (Promega) and precipitated with ethanol. Reverse transcription was performed as described by Pan et al. (2003). PCR was performed in 20 μl reactions containing 2 μl of each reverse transcription products, 1×PCR buffer (TaKaRa), 1.5 mM $MgCl_2$, 300 μM dNTPs, 0.3 μM of each primer (P2L, P2R and P2'L, P2'R), and 2 U Taq DNA polymerase (TaKaRa). PCR amplification conditions of SOCS2 were 4 min at 94°C, followed by 27 cycles of 94°C 40 s, 65°C 40 s, 72°C 40 s and a final extension step of 5 min at 72°C. The PCR amplification conditions of SOCS3 were same to SOCS2 except for 69°C anneal temperature and 30 cycles. GAPDH was used as internal control, which was annealing at 60°C and 27 cycles. Eight microlitre PCR products were used to detect the expression profile on 2.0% agarose gels stained with 0.5 μg/ml ethidium bromides.

Genetic variation identification and traits association analysis of SOCS2 gene

SOCS2 gene polymorphism was detected with PCR-RFLP. A 349 bp genomic fragment was amplified with P3L, P3R. This fragment was digested using *Cfr421* (MBI), which was performed in volume of 10 μl mixture containing PCR products 5 μl, 5 U *Cfr421* (MBI), 1×buffer (MBI), incubated 2 h at 37°C. Different alleles were confirmed by sequencing. One hundred and ninety-eight DNA samples of unrelated pigs from six breeds (Dahuabai, Erhualian, Yushan, Qingping, Large white and Landrace) were genotyped for genetic variation analysis. A chi-squared test on the allele frequencies for these six breeds was performed using SAS 8.1. An experimental population (129 pigs) including two cross-bred groups and three pure-blood groups, Large White×(Landrace×Tongcheng) (24 individuals), Landrace×(Large White×Tongcheng) (23 individuals), Tongcheng breed (31 individuals), Landrace (26 individuals) and Large white (25 individuals), were selected for association analysis. Three economic traits, average day gain (ADG), backfat thickness (BF), lipid content (LC), were selected and analyzed using the general linear model (GLM) procedure, according to the model: $Y_{ij} = \mu+G_i+C_j+e_{ij}$. Y_{ij}, trait measured on animal; μ, mean; G_i, effect of genotype (i = 1, 2, 3); C_j, effect of combination (j = 1, 2, 3, 4, 5); e_{ij}, error term.

Porcine SOCS3 gene full-length coding regions isolation

Two fragments of porcine SOCS3 gene were isolated by RT-PCR. The two fragments were cloned to PGEM-T (promega) clone vector and sequenced. There was a 225 bp overlap region between these two fragments. Therefore, the two fragments were assembled to one contig of 2,122 bp. An open reading frame (ORF) was found and the amino acid sequence was deduced with the program Seqman

Table 2. Mapping results of porcine SOCS2 and SOCS3 genes

Gene symbol	SCHP results (error risk<0.1%)			IMpRH results		
	Regional assignment	Probability	Correlation	Closest mark	Distance (cR)	LOD score
SOCS2	5(1/2 q21)-q24	0.8900	0.9286	Sw1383	47	8.3
SOCS3	12p11-(2/3 p13)	0.8901	1.0000	SW2490	43	8.05

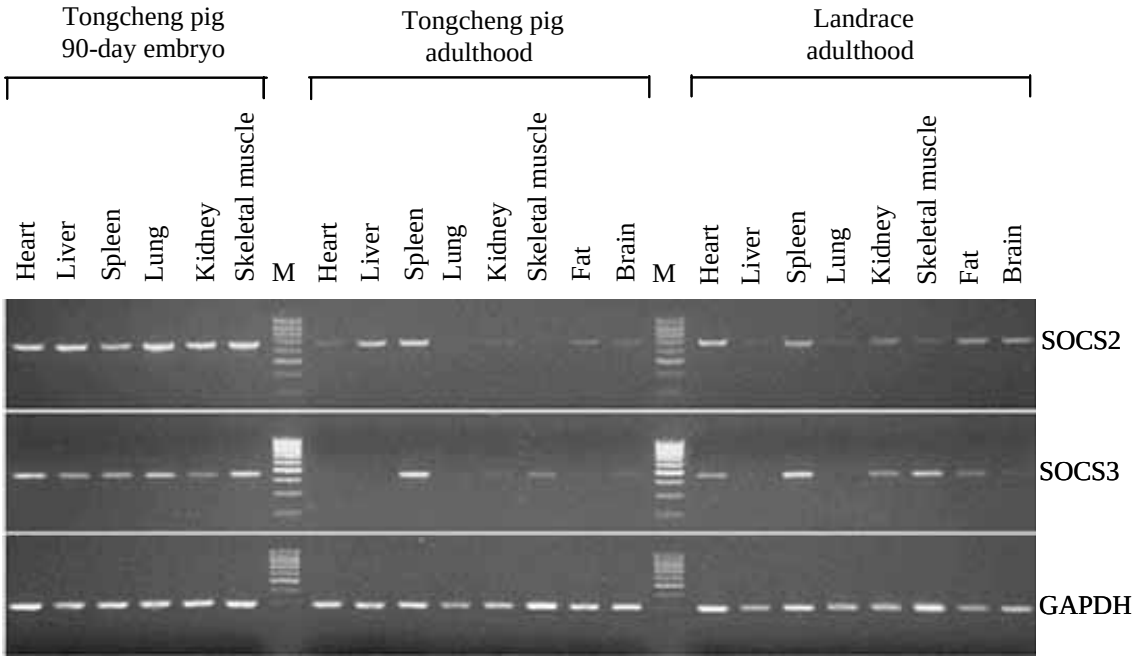

Figure 1. RT-PCR tissue expression analysis of SOCS2 and SOCS3 genes in Heart, Liver, Spleen, Lung, Kidney, Skeletal muscle, Fat and Brain of Tongcheng 90-day embryo, Tongcheng adulthood and Landrace adulthood.

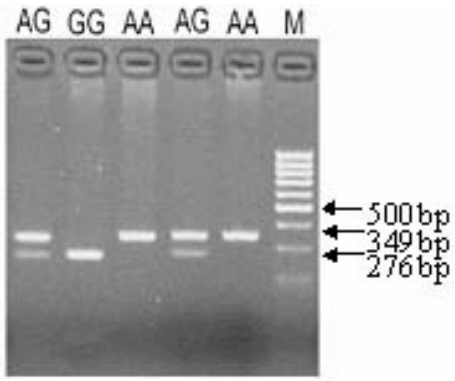

Figure 2. PCR-RFLP (*Cfr421*) analysis and genotypes of porcine SOCS2 gene. The genotypes were indicated on the top of the lanes (M stands for 100 bp DNA ladder).

(DNA star, Madison, WI, USA). Homologous between human and pig was analyzed by BLAST tool available on the web site (http://www.ncbi.nlm.nih.gov/BLAST/).

RESULTS

SCHP and RH mapping of the porcine SOCS2 and SOCS3 genes

Porcine SOCS2 and SOCS3 genes were assigned to SSC5 (1/2) q21-q24 and SSC12p11-(2/3p13) by SCHP analysis respectively. RH mapping allowed the locations of these two genes to be defined more precisely. RH analysis showed that SOCS2 was closely linked with SW1383 marker (distance = 47cR, LOD = 8.3) and SOCS3 was closely linked with SW2490 marker (distance = 43cR, LOD = 8.05). The mapping results were displayed on Table 2.

Tissue distribution of SOCS2 and SOCS3 genes

RT-PCR analysis indicated the expression patterns of SOCS2 and SOCS3 genes. There were at least five points need noticing. Firstly, all six tissues (heart, liver, spleen, lung, kidney and skeletal muscle) of Tongcheng pig 90-day embryo expressed SOCS2 and SOCS3 genes. Secondly, the expression level of SOCS2 gene at 90-day embryo stage was relatively higher than at adulthood. Thirdly, there were weak or no expressions of SOCS2 and SOCS3 genes in many tissues at adulthood. Fourthly, there was higher expression in the liver of adult Tongcheng pig than adult Landrace. In addition, SOCS3 gene expressed high in spleen at adulthood (Figure 1).

Genetic variation identification and association analysis

The 349 bp PCR fragment of porcine SOCS2 gene was sequenced and revealed a G to A transition at position of 72

Table 3. Genotypes and alleles frequency of porcine SOCS2 gene in different breeds, based on the genotyping of the PCR-PFLP (*Cfr421*)

Breeds	N	Genotype			Allele frequency	
		AA	AG	GG	A	G
Dahuabai	32	0	0	32	0	1
Erhualian	32	0	1	31	0.0156	0.9844
Yushan	30	1	4	25	0.1	0.9
Qingping	37	1	18	18	0.2703	0.7297
Large white	35	5	21	9	0.4429	0.5571
Landrace	32	14	17	1	0.7031	0.2969

Table 4. Significance chi-squared test results for the allele frequency distribution among different populations of *Cfr421*-RFLP for the porcine SOCS2 gene

	Dahuabai	Erhualian	Yushan	Qingping	Large white
Erhualian	1.02	-	-	-	-
Yushan	5.80	3.38	-	-	-
Qingping	22.68*	19.40*	9.42	-	-
Large white	38.85**	35.22**	21.50*	5.85	-
Landrace	60.12**	56.35**	41.45**	26.28**	10.97

* Indicates $p<0.05$, ** indicates $p<0.01$.

Table 5. Association analyses of SOCS2 gene *cfr421*-RFLP genotypes with average day gain, backfat thickness and lipid content

Genetypes	Number of animals						Average	Backfat	Lipid
SOCS2-*cfr421*	T	L	Y	LYT	YLT	Total	day gain (g)	thickness (mm)	content (%)
AA	0	3	7	2	4	16	788.96±23.26	30.04±1.18	2.23±0.16
AG	0	11	14	9	13	47	780.34±13.90	31.02±0.70	2.15±0.09
GG	31	12	4	12	7	66	747.58±12.80	31.11±0.65	2.20±0.09
P-value									
AA-AG							0.74	0.46	0.62
AG-GG							0.11	0.94	0.70
AA-GG							0.14	0.45	0.86

bp. Restriction enzyme analysis revealed a polymorphic *Cfr421* site. The two allele-specific patterns obtained after *Cfr421* digestion were an uncut 349 bp fragment for allele A and two fragments of 276 bp and 73 bp (the 73 bp band was too weak to see) for allele G (Figure 2). The analysis of allele frequency distribution revealed that exotic breeds (Large white and Landrace) had higher frequency of the A allele whereas Chinese native breeds (Dahuabai, Erhualian, Yushan, Qingping) had higher frequency of the G allele (Table 3). The statistical analysis indicated a significant difference between Chinese native breeds and exotic breeds (Table 4). Traits association analysis was performed in an experimental population. There were no significant associated between the polymorphism and the three traits (ADG, BF, LC) (Table 5).

Porcine SOCS3 gene coding regions isolation

The 2,122 bp fragment includes a 690 bp ORF, which codes 229 amino acids, was obtained by RT-PCR. The blast results indicated that there was 94% identity homologous between the ORF and human SOCS3 gene ORF (Genbank: NM_003955) and 96% homologous of amino acid sequence. Porcine SOCS3 gene has been submitted to the genebank database (AY944571).

DISCUSSION

Mapping of porcine SOCS2 and SOCS3 genes

In human being, SOCS2 gene was located at 12q21.3-q23 (Yandava et al., 1999) and SOCS3 gene was located at 17q25.3 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=9021). Therefore, porcine SOCS2 and SOCS3 genes mapping results were consistent with human-pig comparative mapping results and the location of porcine SOCS3 was confirmed by Zhao et al. (in press). Porcine SOCS3 gene had been located at the same region by Zhao et al. (in press). Moreover, porcine SOCS2 gene was linked to the important porcine growth factor IGF-1 gene, which was located at 5q23 or 5q25 (http://www.toulouse.inra.fr/lgc/pig/cyto/gene/chromo/SSCG5.htm). Porcine SOCS3 gene was linked to the important porcine growth factor GH gene, which was located at 12q14 (Chowdhary et al., 1994). The information of gene mapping indicated that porcine *SSC5* long arm and porcine *SSC12* short arm may closely related to the porcine growth. On the other hand, SOCS2 and SOCS3 genes link

with important growth genes. Therefore, the result of traits association analysis may influence by these linked genes.

Tissue distribution of porcine SOCS2 and SOCS3 genes

All the tissues studied at 90-day embryo expressed SOCS2 and SOCS3 genes indicated that they expressed broadly at swine embryo middle-late period. SOCS2 gene expressed higher at 90-day embryo then at adult period, which may because that GH expressed higher at embryo then at adulthood. In addition, SOCS2 gene expressed higher in liver of adult Tongchen pig then in liver of adult Landrace. It is well known that liver is the major target organ of growth regulation of GH. Therefore, further study to confirm whether the low growth speed of Tongcheng pig dues to the high expression of SOCS2 gene in liver would be necessary. At spleen tissue of both adult Tongcheng pig and Landrace, SOCS3 gene had higher expression. This implied that SOCS3 gene might play an important role in immunity of pig. In rat, SOCS3 gene had relatively high expression at Lung and spleen tissues (Tollet-Egnell et al., 1999).

Polymorphism and association analysis

An A/G transition was found at 5'-UTR of porcine SOCS2 gene. The allele distribution revealed that the Chinese indigenous breeds had higher frequency of the G allele whereas Landrace had higher frequency of the A allele. The frequency of A allele in Large white was much higher than in Chinese native breeds, Although it was lower than 50%. The difference between domestic breeds and foreign breeds may be mainly responsible for the difference of the allele frequencies. In addition, this site may link with some locus which associated with some traits. Therefore, the allele frequencies changed under the selection (Zeng et al., 2005). As a result, the alleles frequencies differ between domestic breeds and foreign breeds. It is well known that 5'-UTR is the regulation regions of expression. Mutation in this region might affect the expression level of gene, which result in change of the function of gene then influence some phenotype traits. It is a pity that there were no significant associated between the novel SNP and traits studied. We will continue to detect SNPs of SOCS2 and SOCS3 genes in the future in order to find some traits associated SNPs.

Porcine SOCS3 gene full-length coding regions were isolated. SOCS3 gene has very important function, but the complete CDs of porcine SOCS3 gene have not been cloned. According to the conserve regions of mouse SOCS3 gene (Genbank: NM_007707) and human SOCS3 gene (Genbank: NM_003955), a primer (5'-CTCCGTGCGCCA TGGTCA-3') was designed for porcine SOCS3 gene isolation. This primer includes the start code (ATG) of porcine SOCS3 gene. Other primers were designed using porcine ESTs information (NCBI). Porcine SOCS3 gene full-length CDs were finally been cloned. The high homologous between human SOCS3 gene and porcine SOCS3 gene indicated that this result is reliable.

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