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Association analyses of candidate single nucleotide polymorphisms on reproductive traits in swine[1,2]

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ABSTRACT: The ability to identify young females with superior reproduction would have a large economic impact on commercial swine production. Previous studies have discovered SNP associated with economically important traits such as litter size, growth rate, and feed intake. The objective of this study was to test for association of candidate SNP with sow prolificacy reproductive traits in gilts of a Landrace-Duroc-Yorkshire composite population. Association analyses regressed additive (A), dominant (D), and imprinting (I) SNP effects on each trait with an animal model. A carnitine palmitoyltransferase 1A SNP and a glycogen synthase 1 SNP were associated with age at puberty (AP; D = 10 d; $P = 0.0037$ and A = 3.8 d; $P = 0.0078$, respectively). Four *IGF2* SNP were associated with AP as well, having additive or dominant effects (3.2 to 5.8 d; $P \leq 0.0052$). Two mannosidase 2B2 SNP and 2 prolactin receptor (*PRLR*) SNP were also associated with AP. Solute carrier 22, subfamily member 5 SNP was weakly associated with AP (D = 3.9 d; $P < 0.10$). Polymorphisms within glycogen synthase 1 and protein kinase AMP-activated, gamma 3 noncatalytic subunit had associations with ovulation rate. Estrogen receptor (*ESR*) 1, *ESR2*, PPAR γ coactivator 1, and *IGFBP3* SNP were significantly associated with weaning-to-estrus interval. Two *PRLR* SNP were associated with total number of piglets born (A = 0.57 piglets; $P = 0.0095$ and D = 0.61 piglets; $P = 0.0016$, respectively). A SNP within *PRLR* was also associated with number of piglets born alive (D = 0.61; $P = 0.0016$). The PPAR γ coactivator 1 SNP was associated with total number of piglets born (D = 0.38 piglets; $P = 0.0391$) and number of piglets born alive (D = 0.53 piglets; $P = 0.0032$). The SNP within *ESR1* (A = 0.65 piglets; $P = 0.0950$), *ESR2* (A = −0.33 piglets; $P = 0.0176$), *IGF2* SNP (A = −0.26 piglets; $P = 0.0032$), and *IGFBP3* SNP (D = 0.35 piglets; $P = 0.0683$) were associated with number of piglets born dead. A leptin SNP was associated with mummified fetuses (D = 0.09 piglets; $P = 0.0978$). Many of the SNP analyzed in this study are from genes involved in regulation of metabolism, suggesting that there is an important link between physiological events associated with reproduction and energy utilization. Furthermore, these production and growth trait SNP may serve to assist in selection of young females for superior reproductive performance.

Key words: pig, reproductive trait, single nucleotide polymorphism, sow longevity, swine

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INTRODUCTION

Reproductive performance of female pigs is critical to the economic survivability of producers. The lifetime production of a sow is defined as the number of pigs weaned per sow per lifetime. Rodriguez-Zas et al. (2006) reported that a sow must produce on average 4 litters for optimal economics. It has been estimated that 40 to 50% of sows are culled annually with over one-third of these removals attributed to reproduction inadequacies (D'Allaire et al., 1987; Rodriguez-Zas et al., 2003). Roughly 50% of culls attributed to reproduction are from parity 1 or less gilts (Lucia et al., 2000; Engblom et al., 2007). With a large number of animals

[1]Mention of trade name proprietary product or specified equipment does not constitute a guarantee or warranty by the USDA and does not imply approval to the exclusion of other products that may be suitable.

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being culled at younger ages, there is an increased economic demand for females with greater stayability, the potential for a sow to remain in the herd (Stalder et al., 2003).

Primiparous gilts have greater energetic demands associated with growth and energy utilization during critical periods of time such as gestation and lactation, which may have an impact on reproductive and litter trait performances (Britt, 1986; Willis et al., 2003). An ideal situation would be to utilize genetic screening to identify those animals at greater risk of failing in reproductive performance over the average life of the animal or to find those animals that may have the genetic potential for increased longevity. The objective of the current study was to analyze existing and newly reported polymorphisms that have been previously linked to growth, carcass, reproductive, or litter traits, and evaluate their associations with reproductive and litter traits within a Landrace-Duroc-Yorkshire pig line.

MATERIALS AND METHODS

All experimental procedures were reviewed and approved by the US Meat Animal Research Center (**USMARC**) Animal Care and Use Committee.

Animal Population and Sampling

A founder animal population generated from Yorkshire × maternal Landrace (**YL**) were mated with commercially available semen from unrelated Duroc (n = 12) or high-lean Landrace (n = 12) boars. Offspring (Duroc × YL and Landrace × YL) were then reciprocally bred to create a 4-line composite animal (**LDY**; Holl et al., 2008). Inter se matings were continued for 6 generations.

Phenotypic data were collected from the LDY population to allow for association analyses over a course of 6 yr. Age at puberty (**AP**) data were collected on a subset of LDY females. First detected standing estrus was defined as AP. Monitoring of animals for AP began at 150 d of age and continued through 280 d of age over the course of 2 yr (2001–2002) and was then monitored from 180 d of age through 280 d of age in 2005. Detection of estrus was performed once daily using mature boars and fenceline exposure while herdsmen applied back pressure to females to determine receptivity. Females were bred by AI techniques on subsequent estrus during a set breeding season for the USMARC facility. At approximately 110 d of gestation, females were relocated into individual farrowing crates. At farrowing, the following data were collected from 1,417 females: total number of piglets born (**TNB**), number of piglets born alive (**NBA**), number of stillborn piglets (**NSB**), and number of mummified piglets (**MUM**). Average lactation length was 18 d, at which time dams were separated from the piglets, data were recorded for number of piglets weaned by dam (**NUM_WND**), and sows were placed in group pens (20 sows/pen). Weaning-to-estrus interval (**WEI**) was measured as the duration of days after weaning until estrus was detected using back pressure by a herdsman after fenceline boar exposure. For statistical purposes, WEI was analyzed through d 14 postweaning on an individual basis (n = 1,268). Ovulation rate (**OR**) was determined as the number of corpora lutea at time of slaughter after the WEI after the first (n = 365) or second parity (n = 398).

Gilts were fed a corn-soybean meal diet with varying levels of protein based upon stage of development or energy demands. From 12 to 16 wk of age gilts received a grower diet containing 16% protein. Throughout the breeding phase, a diet with 12.5% protein was used. Diets during gestation and lactation consisted of 16.9% protein and returned to 12.5% protein postweaning. Diets were formulated to meet or exceed National Research Council recommendations (NRC, 1998).

SNP Development and Genotyping

Single nucleotide polymorphisms from candidate genes were identified by sequencing or were previously published (Tables 1 and 2). Briefly, sequencing was performed by designing primers for amplification based on sequence data from GenBank for *Sus scrofa IGFBP1* (AB119126), *IGFBP3* (AY464121), carnitine palmitoyltransferase 1A (***CPT1A***; DN131226), PPARγ coactivator 1 (***PPARGC1A***; AY484500), and solute carrier 22, subfamily member 5 (***SLC22A5***; CU372899; nucleotides 114,061–142,680; Table 1). Genomic DNA was isolated from whole blood of 8 sows with unique sires using a saturated salt procedure (Miller et al., 1988). Amplification was performed using Ampli*Taq* Gold (Applied Biosystems, Foster City, CA), 1× of supplied buffer with 1.5 m*M* $MgCl_2$, 200 μ*M* dNTP, 0.33 μ*M* each primer, and 25 ng of genomic DNA in 12-μL reactions. Polymerase chain reaction was performed on a PTC-100 Programmable Thermal Controller machine (MJ Research Inc., Watertown, MA) with appropriate annealing temperatures (Table 1). Quality of amplicon products was verified on a 1.6% agarose gel. The remaining PCR product was prepared for direct sequencing using the amplification primers on an ABI Prism 3730 DNA analyzer (Applied Biosystems; Smith et al., 2000). Subsequent sequence results were transferred into the USMARC database and chromatograms were assembled and analyzed for polymorphism tags (Nonneman and Rohrer, 2003).

The SNP were genotyped using a primer extension assay on the Sequenom MassArray system (San Diego, CA). Amplification primers, as well as probe primers, were designed using the MassArray Assay Design program (Sequenom). Ten-microliter PCR reactions contained 10 ng of genomic DNA, 0.5 U Ampli*Taq* Gold, 1× of supplied buffer with 1.5 m*M* $MgCl_2$, 250 μ*M* dNTP, and 0.4 μ*M* forward and reverse tailed primers (Integrated DNA Technologies, Coralville, IA). The primer extension reaction used 0.6 μ*M* of probe primer (Integrated DNA Technologies) and was performed

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Table 1. Amplification primers designed for SNP identification in 5 candidate genes

Gene[1]	Sequencing ID	GenBank accession	Location within GenBank sequence, bp	Gene region[2]	Primer (leading and lagging, respectively)	Tm,[3] °C
IGFBP1	67168	AB119126	1,325–1,929	5′ UTR and Exon 1	5′-CGGCTCTGTCCCCTACAAC-3′	58
					5′-GGGAGATGGTGGTACCTGTG-3′	57
IGFBP1	67170	AB119126	3,094–3,700	Exon 2	5′-GGCCAAGCCTGAGGTTTAC-3′	56
					5′-TCAAGTTGCACAGGACAAGC-3′	56
IGFBP1	67172	AB119126	4,288–4,888	Exon 3	5′-CTCCTGCAGGTGTTTAGCAA-3′	55
					5′-TAATGGAAGTGCCACTCAGC-3′	55
IGFBP1	67174	AB119126	5,787–6,396	Exon 4	5′-AAGAAGATCCTGGGCTCCAC-3′	57
					5′-GGAATGTTCTGGTGTGGGTTA-3′	55
IGFBP3	67176	AY464121	3,690–4,339	5′ UTR	5′-TCTGGCAAGAGTGAAGACCA-3′	56
					5′-GTGAGCGGCCAATCCTCT-3′	58
IGFBP3	67178	AY464121	4,323–4,960	Exon 1	5′-GATTGGCCGCTCACTGAC-3′	56
					5′-AGGCTTCAGTTTCCCCAAGT-3′	57
IGFBP3	67180	AY464121	7,581–8,188	Exon 2	5′-ATGGTTTCTTGAGGCCAAGC-3′	56
					5′-CATGGCAACACCAGATCCTT-3′	55
IGFBP3	67182	AY464121	8,523–9,029	Exon 3	5′-TCAGAAGGCTGGCTTCCTTT-3′	57
					5′-GAGGCAGGTTTAGGGCTGTA-3′	57
IGFBP3	67184	AY464121	9,761–10,268	Exon 4	5′-CTGCCCAGATGTCCTTTCTC-3′	55
					5′-CAATGCCGGATCCTCAAC-3′	54
CPT1A	67188	CU694814	84,687–84,938	Exon/Intron 14	5′-TTCCATTCCTTTCCGTTCAC-3′	53
					5′-CAAACAGCTCCACCTGCTG-3′	57
PPARGC1A	49176	AY484500	273–757	Exon 8 and 9	5′-CCCACAACTCCTCCTCATAAAG-3′	60
					5′-ATTTCCTGGTCTTGGAGCTGT-3′	60
SLC22A5	67190	CU856105	166,697–167,315	Exon 1	5′-AGCTCAAGAGCCTGCTCAGT-3′	59
					5′-GTGGAGTGTGCGACCTTAAA-3′	55
SLC22A5	67192	CU856105	146,439–146,956	Exon 2	5′-CAAATAGGAAGGCGAGCAAG-3′	54
					5′-TCGTTCTGCTCAGCAAGTGT-3′	57
SLC22A5	67194	CU856105	139,240–139,746	Exon 3	5′-CCCCTCCCTATGTGACTCTG-3′	57
					5′-ATGTGACCAAGGTGCCACAC-3′	58
SLC22A5	67196	CU856105	138,077–138,596	Exon 4	5′-GGGCTTGGAAACCTCAAGAT-3′	55
					5′-GCACAGGGCTGAGAACAAGT-3′	58
SLC22A5	67198	CU856105	136,851–137,344	Exon 5	5′-GCCCCTTGAAATTTTGTGAT-3′	52
					5′-TCCTAAACCCAATCAATTTCTGA-3′	52
SLC22A5	67200	CU856105	134,098–134,618	Exon 6	5′-CCAGCAAGACGCATAAAACA-3′	54
					5′-ATGCACAGGTGACTGGAACA-3′	57
SLC22A5	67202	CU856105	132,437–133,050	Exon 7	5′-TTGCTGGGACACTCTGGAAT-3′	56
					5′-CATAAAGCCCAAGCCATGAT-3′	53
SLC22A5	67204	CU856105	130,689–131,277	Exon 8	5′-CATCAGCTTGGAGGGACATT-3′	55
					5′-GGGAAGGGAAGGCTAAAACA-3′	55
SLC22A5	67206	CU856105	129,463–130,062	Exon 9	5′-CCCATGAGAATCCTGGGAAC-3′	55
					5′-TGAGTGACTTGGAGTCTGCCTA-3′	57
SLC22A5	67208	CU856105	128,869–129,482	Exon 10	5′-GGCAGACTCCAAGTCACTCA-3′	57
					5′-CCTTCAGGTTTTCCCAGACA-3′	55
SLC22A5	67210	CU856105	128,348–128,949	Exon 10	5′-TCAGCGACAGAGACAGAGGA-3′	57
					5′-CGTCATTTTTGGCACTCAGA-3′	53
SLC22A5	67212	CU856105	127,832–128,440	3′ UTR	5′-CGAGAATCACTCCAGCAGAG-3′	55
					5′-GCTTTGCTTTCAGCGGTATC-3′	55

[1]*CPT1A* = carnitine palmitoyltransferase 1A; *PPARGC1A* = PPARγ coactivator 1; *SLC22A5* = solute carrier 22, subfamily member 5.
[2]Refers to the area within the specific gene where the sequence was amplified. UTR = untranslated region.
[3]Identifies the annealing temperature used during amplification of cDNA.

according to the manufacturer's recommendations for hME or iPLEX chemistry (Sequenom). Animals were genotyped with 92 SNP markers (Table 2).

Tissue Sampling and Processing of Genomic DNA

Genomic DNA for subsequent genotyping was purified from tail tissue samples collected at birth or white blood cell samples stored at −20°C until extraction. Isolation of genomic DNA was performed using the Wizard Genomic DNA Purification kit (Promega, Madison, WI) as per the manufacturer's recommendation. Genomic DNA was quantified using a NanoDrop 1000 Spectrophotometer (Thermo Fisher Scientific, Waltham, MA). Ten nanograms of genomic DNA were spotted into 384 well plates, dried down, and stored until genotyped.

Statistical Analyses

To determine differences among phenotypes, statistical analyses were performed using the general linear model (SAS Inst. Inc., Cary, NC). The model for de-

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Table 2. Individual SNP from candidate genes previously identified as associating with production or growth traits

Gene	Marker ID	Allele	Frequency[1] (LDY)	Source	SSC locus	HSA locus	GenBank	dbSNP ID
Acid labile subunit	ALS_1585	T/C	1.0/0	Li et al., 2007	SSC16:q23	HSA16:1,780,600–1,783,656	—	
Acid labile subunit	ALS_2359	T/C	1.0/0	Li et al., 2007	SSC16:q23	HSA16:1,780,600–1,783,656	—	
Acid labile subunit	ALS_2944	A/G	0.996/0.004	Li et al., 2007	SSC16:q23	HSA16:1,780,600–1,783,656	—	
Carnitine palmitoyltransferase 1	67188_100	G/T	0.47/0.53	Sequencing	SSC2:84,708–84,930[2]	HSA11:68,278,932–68,339,518	BV728397	ss95215234
Carnitine palmitoyltransferase 1	67188_128	G/A	0.82/0.18	Sequencing	SSC2:84,708–84,930[2]	HSA11:68,278,932–68,339,518	BV728397	ss95215235
Estrogen receptor 1	ESR1_1665	C/T	0.21/0.79	Munoz et al., 2007	SSC1:	HSA6:152,170,741–152,461,769	—	
Estrogen receptor 1	ESR1_1755	G/A	0.46/0.54	Munoz et al., 2007	SSC1:	HSA6:152,170,741–152,461,769	—	
Estrogen receptor 2	ESR2_949	A/G	0.51/0.49	Munoz et al., 2004	SSC1:34,728–105,141[2]	HSA14:63,769,608–63,819,456	—	
Ghrelin	GHRL_226	A/G	0.05/0.95	Liu et al., 2007	SSC13:153,668–152,583[2]	HSA10:67,804,361–67,804,397~	—	
Ghrelin	GHRL_231	A/G	0.61/0.39	Liu et al., 2007	SSC13:157,036–156,627[2]	HSA3:10,306,489–10,306,852	—	
Ghrelin	GHRL_239	C/A	1.0/0	Liu et al., 2007	SSC13:157,036–156,627[2]	HSA10:63,742,775–63,742,882	—	
Ghrelin	GHRL_265	G/A	0.36/0.64	Liu et al., 2007	SSC13:153,668–152,583[2]	HSA10:67,804,361–67,804,397~	—	
Ghrelin	GHRL_953	C/T	0.61/0.39	Liu et al., 2007	SSC13:153,668–152,583[2]	HSA10:67,804,361–67,804,397~	—	
Glycogen synthase 1	GYS1	G/A	0.23/0.77	Te Pas et al., 2003	SSC6:	HSA19:54,164,586–54,166,090	—	
IGF2	IGF2_14979	C/A	0.69/0.31	van Laere et al., 2003	SSC2:2p	HSA11:2,106,923–2,116,780	—	
IGF2	IGF2_15149	A/G	0.31/0.69	van Laere et al., 2003	SSC2:2p	HSA11:2,106,923–2,116,780	—	
IGF2	IGF2_15584	C/G	0.31/0.69	van Laere et al., 2003	SSC2:2p	HSA11:2,106,923–2,116,780	—	
IGF2	IGF2_17298	C/T	0.29/0.71	van Laere et al., 2003	SSC2:2p	HSA11:2,106,923–2,116,780	—	
IGF2	IGF2_17853	C/T	0.47/0.53	van Laere et al., 2003	SSC2:2p	HSA11:2,106,923–2,116,780	—	
IGFBP1	67170_146	C/T	0.47/0.53	Sequencing	SSC:18q24-qter	HSA7:45,894,484–45,899,792	BV728390	ss95215207
IGFBP1	67170_151	A/G	N/A	Sequencing	SSC:18q24-qter	HSA7:45,894,484–45,899,792	BV728390	ss95215208
IGFBP1	67170_190	G/T	0.45/0.55	Sequencing	SSC:18q24-qter	HSA7:45,894,484–45,899,792	BV728390	ss95215209
IGFBP1	67170_521	C/T	N/A	Sequencing	SSC:18q24-qter	HSA7:45,894,484–45,899,792	BV728390	ss95215210
IGFBP1	67170_576	A/G	0.35/0.65	Sequencing	SSC:18q24-qter	HSA7:45,894,484–45,899,792	BV728390	ss95215211
IGFBP1	67170_90	C/T	0.58/0.42	Sequencing	SSC:18q24-qter	HSA7:45,894,484–45,899,792	BV728390	ss95215212
IGFBP1	67172_665	G/T	0.63/0.37	Sequencing	SSC:18q24-qter	HSA7:45,894,484–45,899,792	BV728510	ss95215213
IGFBP1	67172_680	A/G	N/A	Sequencing	SSC:18q24-qter	HSA7:45,894,484–45,899,792	BV728510	ss95215214
IGFBP1	67174_124	C/T	0.58/0.42	Sequencing	SSC:18q24-qter	HSA7:45,894,484–45,899,792	BV728511	ss95215215
IGFBP1	67174_132	T/C	0.63/0.37	Sequencing	SSC:18q24-qter	HSA7:45,894,484–45,899,792	BV728511	ss95215216
IGFBP1	67174_240	G/T	0.49/0.51	Sequencing	SSC:18q24-qter	HSA7:45,894,484–45,899,792	BV728511	ss95215217
IGFBP3	67176_452	T/A	0.06/0.94	Sequencing	SSC:18q24	HSA7:45,918,484–45,933,148	—	
IGFBP3	67176_777	A/G	0.22/0.77	Sequencing	SSC:18q24	HSA7:45,918,484–45,933,148	BV728395	ss95215218
IGFBP3	67176_789	A/G	N/A	Sequencing	SSC:18q24	HSA7:45,918,484–45,933,148	BV728395	ss95215219
IGFBP3	67178_164	T/C	1.0/0	Sequencing	SSC:18q24	HSA7:45,918,484–45,933,148	—	
IGFBP3	67178_204	G/A	1.0/0	Sequencing	SSC:18q24	HSA7:45,918,484–45,933,148	—	
IGFBP3	67180_1001	T/C	0.44/0.56	Sequencing	SSC:18q24	HSA7:45,918,484–45,933,148	BV728391	ss95215220
IGFBP3	67180_677	A/G	0.002/0.998	Sequencing	SSC:18q24	HSA7:45,918,484–45,933,148	BV728391	ss95215221
IGFBP3	67180_848	C/T	0.52/0.48	Sequencing	SSC:18q24	HSA7:45,918,484–45,933,148	BV728391	ss95215222
IGFBP3	67180_893	A/G	0.44/0.56	Sequencing and Liu et al., 2007	SSC:18q24	HSA7:45,918,484–45,933,148	BV728391	ss95215223
IGFBP3	67180_897	A/C	N/A	Sequencing and Liu et al., 2007	SSC:18q24	HSA7:45,918,484–45,933,148	BV728391	ss95215224
IGFBP3	67180_905	T/C	0.62/0.38	Sequencing and Liu et al., 2007	SSC:18q24	HSA7:45,918,484–45,933,148	BV728391	ss95215225

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Table 2 (Continued). Individual SNP from candidate genes previously identified as associating with production or growth traits

Gene	Marker ID	Allele	Frequency[1] (LDY)	Source	SSC locus	HSA locus	GenBank	dbSNP ID
IGFBP3	67180_933	A/G	0.58/0.42	Sequencing and Liu et al., 2007	SSC:18q24	HSA7:45,918,484–45,933,148	BV728391	ss95215226
IGFBP3	67182_288	C/T	0.61/0.39	Sequencing and Liu et al., 2007	SSC:18q24	HSA7:45,918,484–45,933,148	BV728396	ss95215227
IGFBP3	67182_329	G/A	0.41/0.59	Sequencing	SSC:18q24	HSA7:45,918,484–45,933,148	BV728396	ss95215228
IGFBP3	67184_136	C/T	0.64/0.36	Sequencing and Liu et al., 2007	SSC:18q24	HSA7:45,918,484–45,933,148	BV728512	ss95215229
IGFBP3	67184_375	G/A	0.61/0.39	Sequencing and Liu et al., 2007	SSC:18q24	HSA7:45,918,484–45,933,148	BV728512	ss95215230
IGFBP3	67184_397	C/T	0.69/0.31	Sequencing	SSC:18q24	HSA7:45,918,484–45,933,148	BV728512	ss95215231
IGFBP3	67184_450	G/A	0.51/0.49	Sequencing	SSC:18q24	HSA7:45,918,484–45,933,148	BV728512	ss95215232
IGFBP3	67184_477	A/G	0.14/0.86	Sequencing	SSC:18q24	HSA7:45,918,484–45,933,148	BV728512	ss95215233
Leptin	LEP_2845	T/A	0.34/0.66	Kennes et al., 2001	SSC18:190,329–194,900[2]	HSA7:127,678,829–127,684,023	—	
Leptin	LEP_3469	T/C	0.82/0.18	Kennes et al., 2001; Liu et al., 2007	SSC18:190,329–194,900[2]	HSA7:127,678,829–127,684,023	—	
Leptin	LEP_368	C/T	0.93/0.07	Liu et al., 2007	SSC18:190,329–194,900[2]	HSA7:127,678,829–127,684,023	—	
Leptin	LEP_4280	T/C	0.09/0.91	Liu et al., 2007	SSC18:190,329–194,900[2]	HSA7:127,678,829–127,684,023	—	
Leptin	LEP_4643	G/C	0/1.0	Liu et al., 2007	SSC18:190,329–194,900[2]	HSA7:127,678,829–127,684,023	—	
Leptin	LEP_4890	C/T	0.15/0.85	Liu et al., 2007	SSC18:190,329–194,900[2]	HSA7:127,678,829–127,684,023	—	
Leptin	LEP_554	G/A	0.30/0.70	Liu et al., 2007	SSC18:190,329–194,900[2]	HSA7:127,678,829–127,684,023	—	
Mannosidase 2b2	MAN2B2_1574	G/A	0.36/0.64	Campbell et al., 2008	SSC8:	HSA4:6,627,925–6,672,674	—	
Mannosidase 2b2	MAN2B2_1998	C/A	0.47/0.53	Campbell et al., 2008	SSC8:	HSA4:6,627,925–6,672,674	—	
Melanocortin 4 receptor	MC4R_1426	G/A	0.52/0.48	Kim et al., 2000	SSC1:172,573–173,318[2]	HSA18:56,189,603–56,190,348	—	
Mucin 4	MUC4_243	A/G	0.39/0.61	Peng et al., 2007	SSC13:104,868–105,405[2]	HSA3:196,973,578–196,974,096	—	
Mucin 4	MUC4_344	A/G	0.21/0.79	Peng et al., 2007	SSC13:104,868–105,405[2]	HSA3:196,973,578–196,974,096	—	
PPARγ, coactivator 1	PPARGC1A_SNP3	G/A	0.05/0.95	Sequencing	SSC8:	HSA4:p15.1	—	
PPARγ, coactivator 1	PPARGC1A_SNP4	G/C	0.07/0.93	Sequencing	SSC8:	HSA4:p15.1	—	
PPARγ, coactivator 1	PPARGC1A_SNP5	G/A	0.93/0.07	Sequencing	SSC8:	HSA4:p15.1	—	
PPARγ, coactivator 1	PPARGC1A_SNP8	C/T	0.45/0.55	Sequencing	SSC8:	HSA4:p15.1	—	
PPARγ, coactivator 1	PPARGC1A_SNP9	G/T	0.97/0.03	Sequencing	SSC8:	HSA4:p15.1	—	
PPARγ, coactivator 1	PPARGC1A_SNP10	T/C	0.34/0.66	Sequencing	SSC8:	HSA4:p15.1	—	
PPARγ, coactivator 1	PPARGC1A_SNP12	A/T	0.44/0.56	Jacobs et al., 2006	SSC8:	HSA4:p15.1	—	
PPARγ, coactivator 1	PPARGC1A_SNP13	C/A	0.92/0.08	Jacobs et al., 2006	SSC8:	HSA4:p15.1	—	
Prolactin receptor	PRLR_1217	T/C	0.55/0.45	Tomas et al., 2006	SSC16:	HSA5:35,101,261–35,125,496	—	
Prolactin receptor	PRLR_1439	G/A	0.26/0.74	Tomas et al., 2006	SSC16:	HSA5:35,101,261–35,125,496	—	
Prolactin receptor	PRLR_1528	T/A	0.33/0.67	Tomas et al., 2006	SSC16:	HSA5:35,101,261–35,125,496	—	
Prolactin receptor	PRLR_1789	G/A	0.58/0.42	Tomas et al., 2006	SSC16:	HSA5:35,101,261–35,125,496	—	
Protein kinase, amp-activated gamma 3 noncatalytic subunit	PRKAG3_I199V	A/G	0.12/0.88	Milan et al., 2000	SSC15:q	HSA2:219,401,496–219,403,836	—	
Protein kinase, amp-activated gamma 3 noncatalytic subunit	PRKAG3_T30N	C/A	0.61/0.39	Milan et al., 2000	SSC15:q	HSA2:219,401,496–219,403,836	—	
Protein kinase, amp-activated gamma 3 noncatalytic subunit	PRKAG3_G52S	G/A	0.65/0.35	Ciobanu et al., 2001	SSC15:q	HSA2:219,401,496–219,403,836	—	
Solute carrier protein 22, subfamily A 5	67190_266	A/G	N/A	Sequencing	SSC2:95,302–95,920[2]	HSA5:131,733,343–131,759,202	BV728513	ss95215236

Continued

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Table 2 (Continued). Individual SNP from candidate genes previously identified as associating with production or growth traits

Gene	Marker ID	Allele	Frequency[1] (LDY)	Source	SSC locus	HSA locus	GenBank	dbSNP ID
Solute carrier protein 22, subfamily A 5	67192_120	A/G	0.85/0.15	Sequencing	SSC2:87,547–88,064[2]	HSA5:131,733,343–131,759,202	BV728392	ss95215237
Solute carrier protein 22, subfamily A 5	67192_460	C/T	0.12/0.88	Sequencing	SSC2:87,547–88,064[2]	HSA5:131,733,343–131,759,202	BV728392	ss95215238
Solute carrier protein 22, subfamily A 5	67192_475	G/A	0.70/0.30	Sequencing	SSC2:87,547–88,064[2]	HSA5:131,733,343–131,759,202	BV728392	ss95215239
Solute carrier protein 22, subfamily A 5	67196_144	C/T	0.88/0.12	Sequencing	SSC2:79,231–79,713[2]	HSA5:131,733,343–131,759,202	BV728514	ss95215240
Solute carrier protein 22, subfamily A 5	67198_284	C/T	0.38/0.62	Sequencing	SSC2:77,947–78,457[2]	HSA5:131,733,343–131,759,202	BV728515	ss95215241
Solute carrier protein 22, subfamily A 5	67200_609	C/A	0.88/0.12	Sequencing	SSC2:76,009–75,488[2]	HSA5:131,733,343–131,759,202	BV728516	ss95215242
Solute carrier protein 22, subfamily A 5	67200_705	T/C	0.11/0.89	Sequencing	SSC2:76,009–75,488[2]	HSA5:131,733,343–131,759,202	BV728516	ss95215243
Solute carrier protein 22, subfamily A 5	67200_731	G/A	0.86/0.14	Sequencing	SSC2:76,009–75,488[2]	HSA5:131,733,343–131,759,202	BV728516	ss95215244
Solute carrier protein 22, subfamily A 5	67202_345	A/G	0.11/0.89	Sequencing	SSC2:73,827–74,441[2]	HSA5:131,733,343–131,759,202	BV728517	ss95215245
Solute carrier protein 22, subfamily A 5	67202_705	A/G	N/A	Sequencing	SSC2:73,827–74,441[2]	HSA5:131,733,343–131,759,202	BV728517	ss95215246
Solute carrier protein 22, subfamily A 5	67206_385	C/T	0.29/0.71	Sequencing	SSC2:70,852–71,454[2]	HSA5:131,733,343–131,759,202	BV728398	ss95215247
Solute carrier protein 22, subfamily A 5	67206_472	G/A	0.86/0.14	Sequencing	SSC2:70,852–71,454[2]	HSA5:131,733,343–131,759,202	BV728398	ss95215248
Solute carrier protein 22, subfamily A 5	67206_513	G/C	0.28/0.72	Sequencing and dbSNP[3]	SSC2:70,852–71,454[2]	HSA5:131,733,343–131,759,202	BV728398	ss95215249
Solute carrier protein 22, subfamily A 5	67206_607	C/T	0.15/0.85	Sequencing	SSC2:70,852–71,454[2]	HSA5:131,733,343–131,759,202	BV728398	ss95215250
Solute carrier protein 22, subfamily A 5	67206_786	C/T	0.27/0.73	Sequencing	SSC2:70,852–71,454[2]	HSA5:131,733,343–131,759,202	BV728398	ss95215251
Solute carrier protein 22, subfamily A 5	67208_337	T/C	0.55/0.45	Sequencing	SSC2:70,261–70,872[2]	HSA5:131,733,343–131,759,202	BV728518	ss95215252
Solute carrier protein 22, subfamily A 5	67208_458	C/T	0.87/0.13	Sequencing	SSC2:70,261–70,872[2]	HSA5:131,733,343–131,759,202	BV728518	ss95215253
Solute carrier protein 22, subfamily A 5	67208_564	C/G	0.11/0.89	Sequencing	SSC2:70,261–70,872[2]	HSA5:131,733,343–131,759,202	BV728518	ss95215254
Solute carrier protein 22, subfamily A 5	67208_605	C/A	0.43/0.57	Sequencing	SSC2:70,261–70,872[2]	HSA5:131,733,343–131,759,202	BV728518	ss95215255
Solute carrier protein 22, subfamily A 5	67210_193	C/A	0.73/0.27	Sequencing	SSC2:69,766–70,339[2]	HSA5:131,733,343–131,759,202	BV728519	ss95215256
Solute carrier protein 22, subfamily A 5	67212_246	C/T	0.27/0.73	Sequencing	SSC2:69,222–69,830[2]	HSA5:131,733,343–131,759,202	BV728520	ss95215257
Succinate dehydrogenase complex subunit d	SDHD_444	G/T	0.58/0.42	Guimaraes et al., 2007	SSC9:175,869–136,674[2]	HSA11:111,463,809–111,471,105	—	

[1]Frequency derived from 4-line composite animal (LDY; Holl et al., 2008) population at USMARC. N/A: not available (not genotyped in the LDY population).
[2]Identifies working draft chromosomes.
[3]Accession number ss49857709 in the GenBank dbSNP database.

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termining differences in AP included $Y_{ijk} = \mu + Birth_Year_j + Season_k$. The model for determining differences in OR and WEI included $Y_{ijk} = \mu + Parity_j + Season_k$. Farrowing year and age first mated were excluded from the model because they did not have a significant ($P > 0.10$) effect on OR or WEI. An interaction between season and parity was not evident ($P > 0.10$); therefore, it was removed from the model. Two samples were excluded from the OR data set because they were outliers (OR = 1 and 47). When determining differences for reproductive traits, TNB, NBA, NUM_WND, NSB, or MUM, the model included $Y_{ij} = \mu + Parity_j$. The model for determining differences in traits (TNB, NBA, NUM_WND, NSB, or MUM) by WEI included $Y_{ijk} = \mu + WEI_j + Parity_k$. Phenotypic correlations of WEI with AP and OR were derived.

Founder animals (YL), all sires (Duroc, Landrace, or LDY), and most phenotyped females were genotyped to provide a complete profile for the use of a multilocus version of GenoProb (Thallman, 2002) as a means to calculate the genotypic probabilities for LDY females and to determine parental origin of alleles for heterozygous markers. Seventy-six SNP markers were used for association analyses because the remainder fell out of the total group as a result of nonrobust genotyping (i.e., null alleles detected or a small portion of animals had a detectable genotype; Table 2) or lack of genetic variation within the population.

Heritabilities for performance traits were estimated with a single trait analysis using MTDFREML (Boldman et al., 1995), fitting a complete animal model and appropriate fixed effects including contemporary group and age. Two 2-trait analyses were also conducted to estimate the genetic correlations of WEI with OR and AP. Genotypic probabilities predicted by GenoProb were used to compute regressors for additive, dominant, and alternate heterozygote effects. These regressors were then fitted along with a fixed effect of contemporary group in an animal model for each assay separately. A 3 df *F*-ratio was determined for each test by combining sums of squares for all 3 genotypic effects.

RESULTS

Age at puberty was observed earlier ($P < 0.0001$) in gilts born in 2001 and 2002 in comparison with those females born in 2005 (Table 3). Ovulation rate was greater ($P < 0.0001$) after parity 2 (17.2 ± 0.22; n = 398) vs. parity 1 (15.9 ± 0.17; n = 365). Females that farrowed in November (15.9 ± 0.17; n = 336) had fewer ($P < 0.05$) ova postweaning than those that farrowed in January (17.2 ± 0.25; n = 179) or May (16.7 ± 0.28; n = 155), but were not different ($P = 0.2293$) from those that farrowed in July (16.2 ± 0.34; n = 93). Ovulation rates after July farrowing were also less ($P = 0.0321$) than OR from January-farrowed females. Weaning to estrus interval decreased ($P = 0.0067$) after the second parity (5.65 ± 0.15 d; n = 385) in contrast to parity 1 (6.30 ± 0.12 d; n = 883). The WEI was greater ($P \leq 0.0847$) after farrowing in November (6.4 ± 0.12 d; n = 312) in contrast to those that farrowed in January (5.8 ± 0.19 d; n = 165), May (6.0 ± 0.15 d; n = 416), or July (5.7 ± 0.16 d; n = 375). Weaning-to-estrus intervals were different ($P = 0.0337$) after May and July farrowings. However, WEI after January farrowing was not different ($P > 0.10$) from WEI after May or July farrowings. Total number of piglets born, NBA, and NUM_WND did not influence ($P > 0.10$) WEI of females regardless of parity. Nearly all litter traits improved ($P < 0.005$) with increased parity except for mummified fetuses (MUM; $P = 0.7301$; Figure 1). Total litter weight born and total litter weight weaned did not influence WEI ($P > 0.10$) regardless of parity.

Table 3. Means and SD of puberty measures

		Age at puberty,[1] d	
Year born	n	Least squares mean	SD
2001	270	211.8	2.22
2002	349	212.4	2.06
2005	358	231.4[2]	1.67

[1]Defined as age at first detected estrus.
[2]Differs within a column ($P < 0.0001$).

Calculated heritabilities for the observed traits were weak to moderate (0.06 to 0.24; Table 4). Weaning-to-estrus interval was genetically correlated with AP by 0.50. Regression analyses indicated that a sow with an increased OR by 1 ova would have a reduction ($P = 0.0002$) of the WEI by approximately 0.09 d. However, the genetic correlation estimated between WEI and OR was nearly 0 (−0.01, Table 4).

Sequencing of 5 candidate genes, *IGFBP1*, *IGFBP3*, *CPT1A*, *PPARGC1A*, and *SLC22A5*, identified 60 SNP. Of these, 53 were genotyped within the LDY population and frequencies have been established (Table 2). Most the SNP resided within intronic regions flanking exons. However, 3 *IGFBP1* SNP (67174_124, 67174_132, and 67174_240) were within the fourth exon, downstream of the coding sequence. One synonymous SNP was found within the coding region of *IGFBP3* exon 2 (67180_677; accession AY464121; nucleotide 7845R).

Ninety-two SNP identified from sequencing, or from the literature, were genotyped in the LDY population of swine. Of these, 16 SNP were removed from the association analyses due to low minor allele frequencies.

When a 3 df marker genotypic effect was fitted, several SNP were associated with reproductive traits (Table 5) or litter traits (Table 6). As the alternate heterozygote contrast was usually negligible, subsequent analyses only fitted additive and dominant marker effects. When the 2 df statistical model was significant ($P < 0.10$), additive and dominant effects with SE were estimated.

Eleven SNP associated with AP were found in *CPT1A* (1 SNP), glycogen synthase 1 (***GYS1***; 1 SNP), *IGF2* (4 SNP), mannosidase 2B2 (***MAN2B2***; 2 SNP),

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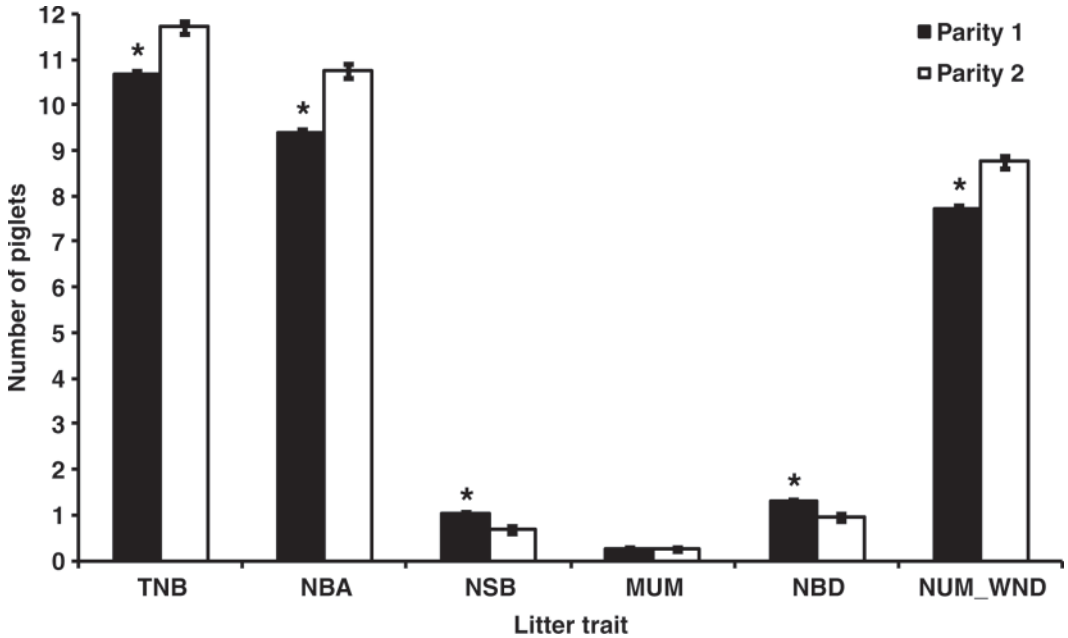

Figure 1. Litter trait characteristics from parities 1 and 2 of the 4-line composite animal (LDY; Holl et al., 2008) population gilts. *Least squares means differ by $P < 0.005$ within trait × parity 1 vs. 2. TNB = total number born; NBA = number of piglets born alive; NSB = number of piglets stillborn; MUM = number of mummified piglets; NBD = number of piglets born dead; NUM_WND = number of piglets weaned by dam.

prolactin receptor (***PRLR***; 2 SNP), and *SLC22A5* (1 SNP; Table 5). The *CPT1A* SNP (67188_128) had a marked association with AP, where heterozygotes had an increased AP of approximately 10 d. A mostly additive effect on AP was observed for a SNP within *GYS1*, yielding an increase of 3.77 d. Of the 4 SNP within the *IGF2* gene (IGF2_15149, IGF2_15584, IGF2_17298, and IGF2_17853) that were associated with AP, additive and dominant effect estimates ranged from 4.36 to 5.79 d for the most significant associations. A SNP within the *MAN2B2* gene exon 10 (MAN2B2_1574) had a dominant effect on AP of −2.30 d, whereas a SNP within exon 12 (MAN2B2_1998) had an overdominant effect of an added 3.44 d to AP. Two SNP within the *PRLR* gene (PRLR_1439 and PRLR_1528) were associated with AP. The *SLC22A5* SNP (67208_605) was weakly associated with AP as the heterozygotes had an increase of approximately 3.86 d.

Single nucleotide polymorphism effects on OR were established for *GYS1*, *IGFBP3*, and protein kinase AMP-activated, gamma 3 noncatalytic subunit (***PRKAG3***) SNP (Table 5). A polymorphism in *GYS1* had an association with OR as a dominant effect of −0.54 corpora lutea. An overdominant effect of −0.78 corpora lutea was observed for the association of an *IGFBP3* SNP (67180_848). A previously reported SNP within *PRKAG3* (PRKAG3_T30N; Milan et al., 2000) also had a significant association, resulting in an additive effect of −0.35 corpora lutea.

A SNP within estrogen receptor (***ESR***)*1* had an additive effect on WEI within the LDY swine population of 1.30 d, whereas heterozygotes for an SNP within *ESR2* had shorter WEI by −0.96 d (Table 5). Furthermore, *IGFBP3* SNP, 67182_329, had a dominant effect of −1.22 d on WEI, whereas the *IGFBP3* SNP, 67184_477, had an overdominant effect of 1.64 d on the

Table 4. Heritabilities and phenotypic variances for traits and correlations between weaning-to-estrus interval (WEI) and ovulation rate (OR) or age at puberty (AP)

Trait	n	Heritability (SE)	Variance
AP	1,000	0.24 (0.08)	298.8
OR	1,011	0.20 (0.07)	9.9
Total number of piglets born (TNB)	1,417	0.19 (0.06)	8.9
Number of piglets born dead (NBD)	1,417	0.15 (0.05)	2.2
Number of piglets born alive (NBA)	1,417	0.19 (0.05)	8.8
Number of piglets mummified (MUM)	1,417	0.06 (0.04)	0.4
Correlation[1]		Genetic correlation (SE)	
WEI and AP		0.50 (0.28)	
WEI and OR		−0.01 (0.22)	

[1]Correlations were computed with 2 trait models in MTDFREML between WEI and the correlated trait.

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Table 5. Association of candidate SNP with reproductive performance traits[1]

Gene[2]	Marker name	Trait	SSC	ADI *P*-value	*F*-value	Effect[3]	Effect *P*-value	Estimate	SE
CPT1A	67188_128	AP	2	0.03644	2.85	A	0.10762	—	—
CPT1A	67188_128	AP	2	0.03644	2.85	D	0.00365	10.03	3.442
GYS1	GYS1	AP	6	0.00496	4.31	A	0.00784	3.77	1.416
GYS1	GYS1	AP	6	0.00496	4.31	D	0.07358	−2.99	1.667
IGF2	IGF2_15149	AP	2	0.00351	4.56	A	0.00211	4.36	1.413
IGF2	IGF2_15149	AP	2	0.00351	4.56	D	0.00069	5.68	1.669
IGF2	IGF2_15149	AP	2	0.00351	4.56	I	0.80891	—	—
IGF2	IGF2_15584	AP	2	0.00421	4.43	A	0.00243	4.52	1.488
IGF2	IGF2_15584	AP	2	0.00421	4.43	D	0.00075	5.74	1.698
IGF2	IGF2_15584	AP	2	0.00421	4.43	I	0.75535	—	—
IGF2	IGF2_17298	AP	2	0.00157	5.14	A	0.00041	5.48	1.544
IGF2	IGF2_17298	AP	2	0.00157	5.14	D	0.00108	5.79	1.765
IGF2	IGF2_17298	AP	2	0.00157	5.14	I	0.31114	—	—
IGF2	IGF2_17853	AP	2	0.04516	2.69	A	0.00522	3.24	1.157
IGF2	IGF2_17853	AP	2	0.04516	2.69	D	0.38493	—	—
IGF2	IGF2_17853	AP	2	0.04516	2.69	I	0.82942	—	—
MAN	MAN2B2_1574	AP	8	0.02601	3.1	A	0.01344	−2.60	1.048
MAN	MAN2B2_1574	AP	8	0.02601	3.1	D	0.09342	−2.30	1.372
MAN	MAN2B2_1998	AP	8	0.03453	2.89	A	0.47595	—	—
MAN	MAN2B2_1998	AP	8	0.03453	2.89	D	0.01571	3.44	1.421
PRLR	PRLR_1439	AP	16	0.00052	5.93	A	0.39544	—	—
PRLR	PRLR_1439	AP	16	0.00052	5.93	D	0.00214	5.25	1.706
PRLR	PRLR_1528	AP	16	0.00850	3.92	A	0.03117	3.31	1.533
PRLR	PRLR_1528	AP	16	0.00850	3.92	D	0.16805	—	—
SLC22A5	67208_605	AP	2	0.03950	2.79	A	0.50053	—	—
SLC22A5	67208_605	AP	2	0.03950	2.79	D	0.09563	3.86	2.315
GYS1	GYS1	OR	6	0.00099	5.47	A	0.08941	−0.40	0.233
GYS1	GYS1	OR	6	0.00099	5.47	D	0.05570	−0.54	0.283
IGF2	IGF2_17853	OR	2	0.02398	3.16	A	0.18476	—	—
IGF2	IGF2_17853	OR	2	0.02398	3.16	D	0.41196	—	—
IGFBP3	67180_848	OR	18	0.00470	4.35	A	0.15298	—	—
IGFBP3	67180_848	OR	18	0.00470	4.35	D	0.00698	−0.78	0.289
PPARGC1A	PPARGC1A_SNP3	OR	8	0.01149	3.7	A	0.28066	—	—
PPARGC1A	PPARGC1A_SNP3	OR	8	0.01149	3.7	D	0.51011	—	—
PPARGC1A	PPARGC1A_SNP12	OR	8	0.04112	2.76	A	0.43773	—	—
PPARGC1A	PPARGC1A_SNP12	OR	8	0.04112	2.76	D	ND	—	—
PRKAG3	PRKAG3_T30N	OR	15	0.01754	3.39	A	0.06792	−0.35	0.189
PRKAG3	PRKAG3_T30N	OR	15	0.01754	3.39	D	0.32411	—	—
ESR1	ESR1_1665	WEI	1	0.01372	3.57	A	0.00164	1.30	0.410
ESR1	ESR1_1665	WEI	1	0.01372	3.57	D	0.12698	—	—
ESR2	ESR2_949	WEI	1	0.04828	2.64	A	0.18397	—	—
ESR2	ESR2_949	WEI	1	0.04828	2.64	D	0.00837	−0.96	0.363
IGFBP3	67182_329	WEI	18	0.01002	3.8	A	0.00272	−1.18	0.392
IGFBP3	67182_329	WEI	18	0.01002	3.8	D	0.01000	−1.22	0.474
IGFBP3	67184_477	WEI	18	0.02898	3.02	A	0.55519	—	—
IGFBP3	67184_477	WEI	18	0.02898	3.02	D	0.01044	1.64	0.639
PPARGC1A	PPARGC1A_SNP10	WEI	8	0.00451	4.38	A	0.00052	−1.21	0.347
PPARGC1A	PPARGC1A_SNP10	WEI	8	0.00451	4.38	D	0.16213	—	—

[1]AP = age at puberty; OR = ovulation rate; WEI = weaning-to-estrus interval; ND = not detectable.

[2]*CPT1A* = carnitine palmitoyltransferase 1A; *GYS* = glycogen synthase; *MAN* = mannosidase; *PRLR* = prolactin receptor; *SLC22A5* = solute carrier 22, subfamily member 5; *PPAFGC1A* = PPARγ coactivator 1; *PRKAG3* = protein kinase AMP-activated, gamma 3 noncatalytic subunit; *ESR* = estrogen receptor.

[3]A 3 df test was conducted to determine association of candidate SNP with reproductive traits. Only those SNP with an *F*-test $P < 0.05$ are reported. The estimated effects are presented when significant. A = additive; D = dominant; I = imprinting. Only those genes with known imprinting have imprinting effects reported.

WEI (Table 5). A polymorphism in the 3′ untranslated (**UTR**) region of PPARGC1A (PPARGC1A_SNP10) was associated with WEI as well with an additive effect of −1.21 d.

Fewer of the genotyped SNP were associated with litter traits (Table 6). Total number of piglets born was associated with 2 *PRLR* SNP (PRLR_1528 and PRLR_1789), having an additive effect of 0.57 piglets or an overdominant effect of 0.61 piglets, respectively. Similarly, the PRLR_1789 SNP was also associated with NBA, having an overdominant effect of 0.61 piglets. The PPARGC1A_SNP13 was associated with TNB and NBA, having a dominant (0.34 piglets) and an overdominant (0.53 piglets) effect, respectively. The *ESR1* gene had 2 individual SNP that were associated with NBD. Both *ESR1* SNP had additive effects on NBD

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Table 6. Association of candidate SNP with litter trait effects

Gene[1]	Marker name	Trait[2]	SSC	ADI *P*-value	*F*-value	Effect[3]	Effect *P*-value	Estimate	SE
PPARGC1A	PPARGC1A_SNP13	TNB	8	0.01430	3.54	A	0.01731	0.34	0.144
PPARGC1A	PPARGC1A_SNP13	TNB	8	0.01430	3.54	D	0.03909	0.38	0.182
PRLR	PRLR_1528	TNB	16	0.01827	3.36	A	0.00948	0.57	0.219
PRLR	PRLR_1528	TNB	16	0.01827	3.36	D	0.56672	—	—
PRLR	PRLR_1789	TNB	16	0.01391	3.56	A	0.29649	—	—
PRLR	PRLR_1789	TNB	16	0.01391	3.56	D	0.00164	0.61	0.194
PPARGC1A	PPARGC1A_SNP13	NBA	8	0.00155	5.15	A	0.01776	0.34	0.143
PPARGC1A	PPARGC1A_SNP13	NBA	8	0.00155	5.15	D	0.00317	0.53	0.180
PRLR	PRLR_1789	NBA	16	0.01247	3.64	A	0.142	—	—
PRLR	PRLR_1789	NBA	16	0.01247	3.64	D	0.001634	0.61	0.192
ESR1	ESR1_1665	NBD	1	0.04516	2.69	A	0.094966	0.25	0.151
ESR1	ESR1_1665	NBD	1	0.04516	2.69	D	0.894183	—	—
ESR1	ESR1_1755	NBD	1	0.02271	3.2	A	0.017608	−0.33	0.140
ESR1	ESR1_1755	NBD	1	0.02271	3.2	D	0.791623	—	—
ESR2	ESR2_949	NBD	1	0.03845	2.81	A	0.358925	—	—
ESR2	ESR2_949	NBD	1	0.03845	2.81	D	0.304979	—	—
IGFBP3	67176_777	NBD	18	0.01317	3.6	A	0.542912	—	—
IGFBP3	67176_777	NBD	18	0.01317	3.6	D	0.068303	0.35	0.194
Leptin	LEP_2845	MUM	18	0.000142	2.73	A	0.45966	—	—
Leptin	LEP_2845	MUM	18	0.000142	2.73	D	0.09778	0.09	0.057

[1]*PPARGC1A* = PPARγ coactivator 1; *PRLR* = prolactin receptor; *ESR* = estrogen receptor.

[2]TNB, total number born; NBA, number of piglets born alive; NBD, number of piglets born dead; MUM, number of mummified piglets.

[3]A 3 df test was conducted to determine association of candidate SNP with various litter trait effects. Only those SNP with an *F*-test *P*-value of <0.05 are reported. The estimated effects are presented when significant. A = additive; D = dominant.

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with ESR1_1665g SNP of 0.25 and ESR1_1775i SNP effect of 0.33 piglets. The *IGFBP3* SNP, 67176_777, had an overdominant effect on NBD with an increase in dead piglets of 0.35 in heterozygous females. A weak association between MUM and a leptin SNP (LEP_2845) was identified; heterozygotes had an estimated increase of 0.09 piglets.

DISCUSSION

Identifying quantifiable traits to measure the potential reproductive performance of young gilts would provide an added benefit for replacement selection practices. However, monitoring AP to identify those animals that could be incorporated into production systems at a younger age would be an extremely labor-intensive venture for large production operations. Numerous traits have been investigated for SNP and their relationship to growth traits in swine. Several of these gene products can be physiologically linked to reproductive variables, as well as to measurements such as feed intake and growth rate. Likewise, larger litter sizes impose greater demand on energy reserves of the sow even under a full-feed situation (Quesnel et al., 2007). A link is believed to exist between postpartum nutritional status and reproductive performance, such as return to estrus (Zak et al., 1998; van den Brand et al., 2000). Therefore, it would prove economically beneficial if genomic tools could be used to identify those animals at a younger age with increased stayability potential.

In the current study, AP differed across years. Specifically, the first 2 yr observed had younger ages of first detected estrus than the later year. This observation is largely a result of a delay in age at which boar exposure and monitoring for first estrus began (approximately 150 vs. 180 d of age). It has been previously reported that most prepubertal gilts older than 140 d of age will respond to boar exposure (Flowers, 1993). van Wettere et al. (2006) reported an earlier age at first estrus when boar exposure was initiated at 161 d of age in comparison with 182 or 203 d of age in Large White × Landrace gilts.

Several reproduction and litter traits were different between parity 1 and 2 within the LDY population. We have reported increased OR as parity increased, which is consistent with other studies (Clark et al., 1972; Deckert et al., 1997). Weaning-to-estrus interval diminished from parity 1 to parity 2. Others (Maurer et al., 1985; Esbenshade et al., 1986; Tummaruk et al., 2001) have also shown decreases in WEI between primiparous and multiparous females with a 25- to 30-d lactation length. Lactation length does influence WEI, as do several other factors (Almond, 1992; Xue et al., 1997). However, the trend among all of these studies suggests that regardless of lactation length, parity influenced WEI. An increase in TNB, NBA, and NUM_WND from parity 1 to parity 2 was reported in the current study, similar to other studies between primiparous and multiparous sows that reported increased TNB and NUM_WND (Tummaruk et al., 2001; Rodriguez-Zas et al., 2003). Furthermore, both studies showed that TNB increased after parity 1 as well. Our data do not find any influence of TNB, NBA, or NUM_WND on the subsequent WEI, which is unlike what was reported by Maurer et al. (1985). In the latter study, use of cubic and quadratic equations provided support for an effect of NBA and NUM_WND on the subsequent WEI; however, we did not see such an effect when these calculations were incorporated (data not shown).

Seventy-eight SNP were genotyped within the LDY population, and association analyses were conducted against several phenotypes. Both *CPT1A* and *SLC22A5* are linked to energy metabolism. Intracellular carnitine is necessary for long-chain fatty acid uptake into the mitochondria for β-oxidation (Koepsell et al., 2007). Periods of increased stress or energy demand require increased carnitine transport to support the β-oxidation pathway for proper metabolic function. Carnitine O-palmitoyltransferase is an enzyme that facilitates the conversion of carnitine to acylcarnitine, which can then be used to produce Acyl-CoA by CPT2, subsequently entering the β-oxidation pathway. Increased expression of *CPT1A* mRNA was associated with fatty acid β-oxidation and gluconeogenesis in periparturient dairy cattle on a feed-restricted diet in comparison with ad libitum-fed cattle (Loor et al., 2006). Similarly, the *SLC22A5* gene product assists with the transport of carnitine into cells, which is necessary for the breakdown of fats. Certain SNP within the *SLC22A5* gene have been associated with autoimmune disorders such as Crohn's disease and ulcerative colitis (Koepsell et al., 2007). The *SLC22A5* gene is ubiquitously distributed in tissues, including reproductive tissues, testis, Sertoli cells, uterus, and placenta, as well as neuronal glial cells. Mote et al. (2009) analyzed SNP markers within *CPT1A* and *SLC22A5*. Markers from both genes suggested an association with stayability of a sow within a herd through the fifth parity. Furthermore, the same favored genotype for stayability of *CPT1A* was also associated with an increase in NBA after the third parity. Within our study, 2 SNP, one within *CPT1A* and the other within *SLC22A5*, had dominant effects resulting in the potential to increase AP. Neither of these SNP were identical to those reported by Mote et al. (2009), but it may imply that alterations to these genes have a direct or indirect role in the maturation of females as a result of altered energy metabolism during the critical phase of growth or that these SNP may be in linkage disequilibrium with a causative polymorphism in another gene.

Peroxisome proliferator activated receptor gamma, coactivator 1A can coactivate the nuclear receptor PPARγ, which affects adipocyte differentiation (Puigserver et al., 1998). This transcriptional coactivator functions to link nuclear receptors to the transcriptional programming necessary for adaptive thermogenesis (Puigserver et al., 1998). Body weight and composition are influenced by adaptive thermogenesis (Dulloo and

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Samec, 2001). Jacobs et al. (2006) reported an SNP within exon 8 of *PPARGC1A* and its association with carcass composition traits such as leaf fat weight, backfat thickness, and belly weight in a Meishan cross population. Therefore, we genotyped previously reported SNP (Jacobs et al., 2006) and additionally sequenced and genotyped SNP within PPARGC1A to determine their associations with reproduction and litter traits. An SNP within exon 9 (PPARGC1A_ SNP13) was associated with TNB and NBA, whereas a polymorphism within the 3′UTR (PPARGC1A_SNP10) was associated with the WEI event. Wilkie et al. (1999) reported a QTL for number of corpora lutea on SSC 8, relative position 50 to 70 cM (according to the USMARC genetic map); *PPARGC1A* lies just forward of this region at approximately 34 cM.

Glycogen synthase 1 also had a dominant effect on AP. There are no reported QTL on SSC 6 associated with AP, but rather potential reproductive QTL for teat number and litter size (Buske et al., 2006) are within close proximity to *GYS1*. However, several QTL for carcass and meat quality have been localized to the same region as *GYS1* (de Koning et al., 1999; Ovilo et al., 2000; Sato et al., 2003). Specifically, QTL have been mapped to SSC 6 for backfat thickness and weights of shoulder and belly bacon (Varona et al., 2002; Ovilo et al., 2005). If an association for AP does exist on SSC 6, it may be related to energy storage, such as backfat thickness and shoulder and belly bacon weights that are necessary to support initiation of reproductive function. In a recent report, gilts attaining puberty earlier (185 d or less) had a greater growth rate during rearing, greater backfat thickness at 200 d of age, and produced more piglets from parities 1 to 3 without an increased removal rate (Young et al., 2008). Earlier accounts by Gaughan et al. (1997) also reported that animals with greater fat deposition and protein deposition attained puberty sooner.

The IGF system has long been associated with growth and reproduction and is composed of 2 primary proteins, IGF-1 and IGF-2, along with 6 IGFBP, an acid labile subunit, and 2 receptors. Biological effects of the IGF system include increased glucose uptake, antiapoptotic activity, and stimulation of DNA, RNA, and protein synthesis (Etherton, 2004). In the current study, we identified 9 individual SNP within the IGF system that were associated with various reproduction or litter traits. Four polymorphisms within the *IGF2* gene were associated with increased AP. Also, an SNP in the predominant binding protein for the IGF system, *IGFBP3*, was associated with OR and WEI. An *IGFBP3* SNP appears to have an overdominant negative effect on the number of corpora lutea, whereas 2 individual SNP for *IGFBP3* had significant effects on WEI. Finally, an *IGFBP3* SNP was associated with an increase in number of piglets born dead within the LDY population. Previous reports have shown that SNP within *IGF2* are related to growth traits in swine (van Laere et al., 2003; Jungerius et al., 2004; Vykoukalova et al., 2006). Several IGF system SNP have been discovered (Li et al., 2007; Liu et al., 2007), but no association analyses were reported by these investigators. However, Mote et al. (2009) reported SNP within IGFBP that were associated with number born alive (*IGFBP*-1 and -2) and stayability through parity 5 (*IGFBP*-1 and -3).

The MAN2B2_1574 SNP and MAN2B2_1998 putatively affected days to puberty. Campbell et al. (2008) reported associations within a Meishan-cross population for SNP within the *MAN2B2* gene and OR with the strongest association with MAN2B2_1574. We, however, did not see an effect of SNP on OR within this study. An association with AP may exist within the Meishan-cross population, but it was not analyzed in the previously cited study. Reported QTL for AP are present on SSC 8 at approximately 101 to 172 cM (Rathje et al., 1997; Cassady et al., 2001; Holl et al., 2004); however, *MAN2B2* lies at 6 to 7 cM on SSC 8.

Early PRLR association studies found no additive or dominant effects associated with NBA, MUM, or NSB fetuses among selection lines for OR and litter size or control line animals (Linvillle et al., 2001). However, similar to our results, van Rens and van der Lende (2002), showed an association of *PRLR* SNP with AP, as well as TNB and NBA. Other reports further support the location of a QTL on SSC 16 for NBA (Vincent et al., 1998; Drogemuller et al., 2001; Tribout et al., 2008).

Two other SNP (GYS1 and PRKAG3_T30N) had significant effects on OR within the LDY population. Glycogen synthase 1 maps to SSC 6; however, only a litter size QTL at approximately 90 to 120 cM has been published (Wilkie et al., 1999), which covers the region of the leptin receptor gene. Chen et al. (2004) reported an association between the leptin receptor gene and litter size, but did not elucidate a causative mutation. Linkage mapping estimates the location of glycogen synthase to be at approximately 79 cM, which lies in close proximity to the putative litter size QTL; however, no QTL for OR has been reported in this region or chromosome. A putative QTL on SSC 15 at 53 to 102.5 cM has been reported for OR with overlap by independent investigators (Rathje et al., 1997; Rohrer et al., 1999; Wilkie et al., 1999). Protein kinase, AMP-activated gamma 3 noncatalytic subunit (***PRKAG3***) maps to 81 to 84 cM on SSC 15. The PRKAG3_T30N SNP was associated with OR in the LDY population, but is likely to be in linkage disequilibrium rather than the causal mutation.

The *ESR* genes had SNP that appear to affect WEI and NBD. Polymorphisms within ESR1_1665 and ESR2_949 had significant associations with WEI. A recent report by Mendoza et al. (2008) found a potential epistatic interaction between *ESR1* and *ESR2* SNP with age at menarche in Spanish women. A QTL for AP has been putatively identified on SSC 1, but it is not within the region of the *ESR* genes (Rohrer et al., 1999). No data to date have associated *ESR* SNP with WEI. Within our population, we found an asso-

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ciation of 2 *ESR1* SNP (ESR1_1665 and ESR1_1755) with NBD. We did not identify any associations of *ESR* SNP with other litter traits within our population. Literature, however, suggests that *ESR* SNP influence litter size traits, such as TNB, NBA, and NUM_WND; however, it is disputed as to whether specific alleles have favorable or unfavorable effects (Rothschild et al., 1996; Goliasova and Wolf, 2004; Munoz et al., 2007). Inconsistencies among literature results can be partially attributed to environmental (including management techniques), genetic, sample size, and phase differences.

A subtle effect on mummified fetuses was observed for LEP_2845 SNP within the leptin gene. No QTL have been described for SSC 18 where the leptin gene resides. Holl et al. (2004) suggested QTL for MUM were evident on SSC 6 and 12.

In conclusion, it is unlikely that the tested candidate SNP are directly influencing the specific reproductive traits analyzed. The data collected suggest that there may be some linkage disequilibrium between SNP genotyped and causative genetic variation affecting reproductive traits within regions previously found to be associated with growth, litter, and reproductive traits. Isolated causal SNP or SNP in LD can then be used for marker-assisted selection among young females to determine those with favorable reproductive performance, which subsequently may influence sow longevity and herd management.

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