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Identification of potential genetic variants associated with longevity and lifetime production traits in a Thai Landrace pig population using weighted single-step genome-wide association methods

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ABSTRACT. Longevity and lifetime production traits are of increasing importance in swine breeding schemes worldwide because these traits influence sow productivity and welfare, as well as affecting farm profitability. The Landrace breed makes up one-half of the F_1 Large White x Landrace female, which is the most popular maternal line in the breeding herd of commercial pork production systems in Thailand and throughout the world. The objective of this study was to estimate genetic parameters and detect potential genetic variants associated with age at first farrowing (AFF), length of productive life (LPL), lifetime number of piglets born alive (LNBA), lifetime number of piglets weaned (LNW), lifetime wean to first service interval (LW2S) and lifetime pig efficiency (LTP365) in a Thai Landrace pig population. dData were analyzed for 82,346 litters from 12,843 Landrace pigs housed in three farms; all farms were a part of a large commercial production system. Genetic parameters were estimated using a single-step, genomic-BLUP (ssGBLUP) that utilizes general pedigree and genomic relationships. Landrace sows

were genotyped with 60K Illumina PorcineSNP60 BeadChip. The genotypes were analyzed by weighted single-step genome-wide association analyses. Heritability estimates for longevity and length of productive life traits were low and ranged from 0.01 to 0.11. The greatest genetic correlations between LPL with LNBA, LNW, LW2S and LTP365 ranged from 0.44 to 0.91. The greatest genetic correlations between LPL and LNBA, LNW, LW2S and LTP365 ranged from 0.44 to 0.91. Based on these results, genetic selection for LPL was not antagonistic with lifetime production. Twenty-seven candidate genes were identified as being associated with one or more traits evaluated in this Landrace pig population. Highlighted genes related to LPL, LNBA, LNW and LTP365 included *TMLHE*, *PDHX* and *KCNJ6* on SSC13 in this pig population. This constitutes a list of candidate genes that could be incorporated into selection to improve sow longevity and lifetime production traits in the pig industry.

Key words: GWAS; Single-step GBLUP; Lifetime production traits; Longevity; Thai Landrace

INTRODUCTION

The Landrace breed or line is one of the maternal breeds used by the Thai commercial pork production industry. The Landrace breed makes up one half of the crossbred sow (F_1) that is most commonly used by Thai commercial pork producers and by pork producers throughout the world. The F_1 Large White x Landrace commercial female is popular because of its superior maternal fertility and fecundity performance. It also maximizes heterosis or hybrid vigor for both the maternal line and the terminal offspring (when the F_1 sow is mated to a terminal sire line from completely unrelated breeds or genetic lines), and because the breeding system to generate the F_1 is easy to implement. However, purebred Landrace pigs have disadvantages, including leg soundness (Huang et al., 2003), which can negatively impact sow longevity and productivity. Sow longevity is an economically important trait for commercial swine farms. This trait not only impacts sow herd productivity but grow–finish pig performance as well. Ultimately, improving sow longevity will increase farm profit and animal welfare by reducing replacement costs and reducing grow–finish and breeding herd lameness. Stalder et al. (2003) suggested that a sow should remain in the breeding herd for at least three parities to pay for itself. Sow longevity can be improved by selecting directly on length of productive life or traits that have a favorable genetic correlation with longevity. Generally, longevity measures include stayability to a constant age, length of productive life (LPL), which can be defined as the number of days between the first insemination or first farrowing and last farrowing, total number of parities produced before culling, lifetime productivity traits (lifetime pig production, lifetime pig efficiency, lifetime litter efficiency), and pigs produced per day of life (Hoge and Bates, 2011). Longevity traits such as LPL are complex traits related to other traits such as number of piglets born alive and weaned, farrowing interval, feet and leg structure and body conformation traits. In addition, age at first farrowing or age at puberty are predictive traits for sow longevity and lifetime productivity. Because the sow longevity

and lifetime productivity traits are measured at the end of the animal's life, it would be beneficial to be able to use genomic or marker-assisted selection to improve these traits.

Recently, highly dense single nucleotide polymorphism (SNP) chips have become commercially availability and genome-wide association analyses (GWAS) can be used to identify genes for complex traits. Moreover, the SNP chips have been applied in commercial breeding programs to estimate genomic breeding values (GEBVs) and implement genomic selection in a breeding program. Misztal et al. (2009) proposed a single-step genomic BLUP (ssGBLUP) for genomic evaluation that combines traditional phenotypic, typical pedigrees and new genomic information including genomic pedigree and genetic information related to specific economically important traits. Furthermore, ssGBLUP is suitable for multiple-trait analyses (Chen et al., 2011). The ssGBLUP has been used when estimating breeding values for several species including dairy (Tsuruta et al., 2011), pigs (Christensen et al., 2012), and chickens (Chen et al., 2011). More recently, GWAS based on ssGBLUP, which called single-step GWAS (ssGWAS) (Wang et al., 2014), was used in place of more traditional GWAS approaches because the latter does not directly use phenotypes from non-genotyped individuals. The weighted single-step GBLUP (WssGBLUP) method were developed in order to estimate the weights for SNP markers within ssGBLUP, which enhances accuracy and precision when estimating SNP effects in GWAS and GEBVs (Zhang et al., 2010). Therefore, GWAS can be useful to identify genomic regions or quantitative trait loci (QTL), which were associated with longevity and lifetime production traits in a Thai pig population. The objective of this study was to estimate genetic parameters and detect potential genetic variants associated with of age at first farrowing (AFF), length of productive life (LPL), lifetime number of piglets born alive (LNBA), lifetime number of piglets weaned (LNW), lifetime wean to first service interval (LW2S) and lifetime pig efficiency (LTP365) in a Thai Landrace pig population.

MATERIAL AND METHODS

Animal care

No Institutional Animal Care and Use Committee (IACUC) approval was needed since the data used for this study were obtained from an existing database.

Animals and phenotype data

The data used in this study were obtained from three farms from a large commercial production system located in central and northeastern Thailand. The data were collected from Landrace pigs during the period from 2006 to 2015 and extracted from the SowTracker® (Version 3.4.2) reproductive data management software. Data were edited to include records with age at the first farrowing range from 280-460 days, weaning age from 19-21 days, and days from weaning to successful breeding from 0-60 days. The sow longevity traits included length of productive life (LPL) which was defined as the number of days between the animal's (female) birthdate to last farrowing date. Age at first farrowing (AFF), lifetime number of piglets born alive (LNBA), lifetime number of piglets weaned (LNW), lifetime wean to first service interval (LW2S) and lifetime pig efficiency (LTP365) was calculated as the lifetime pig production (the number of piglets born alive

during a sow's lifetime) divided by the length of productive life × 365. Animals with incomplete phenotypic (AFF, LPL, LNBA, LNW, LW2S and LTP365) information were removed from the analyses. After data editing, 82,346 litters from 12,843 Landrace (LR) sows with production records remained.

Animal management and nutrition

The number of sows in each herd was approximately 2,500. The sows were housed in an evaporative-cooled housing system (EVAP). The selection objective for these herds is to improve economic traits, including selection to improve reproductive traits (number of pigs born alive: NBA) and growth traits (days to 104 kg: DAYS and percent lean: PCL). The selection index is calculated based on the economic weights and EBVs of the traits (NBA, DAYS and PCL). Breeding values for NBA were estimated using single trait analysis. Whereas, DAYS and PCL were estimated using multiple trait analysis where a BLUP animal model was implemented to analyze these data.

Replacement gilts were visually examined to determine their structural body conformation (feet, legs, >14 functional teats and external genitalia) by experienced staff. Selection criteria were applied to the replacement gilts. The pre-selection started in the nursery stage when gilts having structural defects and hernias, or ruptures were eliminated from consideration. The final selection at approximately 126-147 days of age was based on visual evaluation of feet and leg structure, underline, and external genitalia. Gilts with high selection index score and desirable visual traits entered the gilt pool. After selection, gilts were housed in groups with partially slatted floors. The gilts were provided 2 m^2 (15-20 pigs per pen) floor space allowance per animal. The experienced staff and vasectomized boar were used to determine which gilts were in standing estrus, twice daily at 8.00 and 16.00. Gilts were first inseminated at approximately 35 weeks of age or at their second observed estrus cycle. Sows were inseminated using intrauterine artificial insemination (IUI) procedures using semen from the AI station (within farm). Gilts were moved from gestation units to farrowing units, approximately 5–7 d before the expected farrowing date. Information about total pigs born, number of piglets born alive and mummified piglets were recorded at each farrowing. Pigs were weaned at 19-21 days of age.

At all phases of production / reproductive cycle, gilts and sows were fed a pelleted diet. During gilt development, gestation, and farrowing the diets met or exceeded National Research Council (2012) recommendations for each phase of production. All three farms involved in this study obtain all pig diets from a company owned feed mill and followed standard formulations for all farms in the production system. The gilts were fed 1.8-2.0 kg/day of a 14% crude protein and 2,950 kcal/kg ME diet. Gilts and sows were fed 1.8-2.0 and 2.0-2.4 kg feed/day during weeks 3 and 12 of gestation, respectively. And then, gilts and sows were fed 3 kg feed/day until 3 days before expected farrowing. Finally, the amount of feed was reduced to 2 kg feed/day until the sow farrowed. Lactating sows were fed 3-4, 5, and 6-7 kg feed/day during weeks 1, 2 and 3 of lactation, respectively. Sows and gilts were fed according to body condition determined by visual appraisal (1 = emaciated, 2 = thin, 3 = ideal, 4 = fat and 5 = Obese) (Patience et al., 1995). After weaning, the sows were moved to the mating/gestating units, the sows were fed 1.8-2.0 kg feed/day. All gestating and lactating sows were provided ad-libitum access to water. The gestating sows were fed once daily at 06:30 and lactating sows were fed at 06:30 and 16:00. Additionally,

gilts and sows were removed from the herd if they had three or more failed estrus cycles where each they did not conceive and returned to estrus, developed locomotion problems (injury and lameness) and/or were identified as having a disease problem (vulvar discharges, respiratory problem, prolapse, etc).

Genotype data editing before GWAS

One-hundred forty Landrace pigs were genotyped for 61,177 SNPs. The genotype was determined using the Illumina PorcineSNP60 BeadChip (Illumina Inc., San Diego, CA, USA). The SNP quality control criteria implemented as follows: The individual samples and the SNPs with a call rate < 0.90, SNPs with minor allele frequency < 0.05 and monomorphic SNPs, parent-progeny Mendelian conflicts and the SNPs with unknow the position were excluded from the dataset. A total of 41,609 SNPs and 131 animals were remained in the dataset for genome-wide association analyses using a WssGBLUP (Wang et al., 2012).

Genomic parameter analysis

Genetic parameters (heritability and genetic correlations) with genomic information for longevity and lifetime production traits were estimated using the average information restricted maximum likelihood algorithm implemented in AIREMLF90 program (Misztal et al., 2002). A multivariate linear animal model was implemented using the BLUPF90 software. The model used was as follows:

$$y = X\beta + Za + e, \quad \text{(Eq. 1)}$$

where y is the vector of observations of 6 traits AFF, LPL, LNBA, LNW, LW2S and LTP365; β is the vector of fixed effects that included contemporary groups (herd-year-season interaction); a is the vector of additive direct genetic effect; e is the vector of residual effects. X and Z are incidence matrices. The random effect vectors *a* and *e* were assumed $a \sim N(0, A \otimes G_0)$ and $e \sim N(0, I \otimes R_0)$, respectively, where G_0 and R_0 are additive genetic and residual variance-covariance matrix across 6 traits, I is the identity matrix, $\otimes$ is the Kronecker product operator and A is the pedigree-based relationship matrix. In the ssGBLUP model (Misztal et al., 2009; Christensen and Lund, 2010), A^{-1} matrix was replaced by H^{-1} matrix; H is a matrix that combines pedigree and genomic relationships as in Aguilar et al., (2010) and H inverse is:

$$H^{-1} = A^{-1} + \begin{bmatrix} 0 & 0 \\ 0 & G^{-1} - A_{22}^{-1} \end{bmatrix}, \quad \text{(Eq. 2)}$$

where A^{-1} is the inverse numerator relationship matrix for all animals; A_{22}^{-1} is the inverse of a pedigree-based relationship matrix for genotyped animals; and G^{-1} is the inverse genomic relationship matrix. The genomic relationship matrix G was constructed based on VanRaden (2008) as below:

$$G = \frac{ZDZ'}{2\sum p_i(1-p_i)}, \quad \text{(Eq. 3)}$$

where G is the genomic relationship matrix, Z is a matrix relating genotypes of each locus, D is a diagonal matrix of weights for variances of SNP effects and p_i is the second allele frequency of the i[th] SNP marker.

Single-step genome wide association studies

The WssGWAS were analyzed using the BLUPF90 family software (Misztal et al., 2002), the model is similar to the ssGBLUP. In this study, the SNP solutions were performed by 2 iterations, the weight for each SNP was calculated by recomputing only the SNP effects (Wang et al., 2012). The SNP effects were obtained from GEBV, which was calculated as:

$$\hat{u} = DZ'G^{-1}\hat{g}, \quad \text{(Eq. 4)}$$

where $\hat{u}$ is the vector of estimated SNP effects and $\hat{g}$ is the vector of the additive genetic effect of genotyped animals and $D = I$ for the 1[st] iteration.

The algorithm for computing SNP solutions was as follows: 1. Set t=0 and the weight matrix $D = I$; 2. Compute GEBVs using the ssGBLUP approach by $\hat{g} = Z\hat{u}$; 3. Compute SNP effects $(\hat{u})$; 4. Compute weight for each SNP is based on SNP effect as $d_{ii}^{(t+1)} = \hat{u}_i^2 2p_i(1-p_i)$, where i is the i[th] SNP marker; 5. Normalize $D^{(t+1)}$; 6. Compute weight genomic relationship matrix; and 7. Iterate from 3 until t − 1 = 2. The percentage of genetic variance explained by the i[th] SNP was calculated as follows (Wang et al., 2012):

$$\frac{Var(Z_j\hat{u}_j)}{\sigma_a^2} \times 100\%, \quad \text{(Eq. 5)}$$

where σ_a^2 is the total genetic variance, Z_j is a vector of the gene content of the j[th] SNP for all animals, and $\hat{u}_j$ is the SNP marker effect of the j[th] SNP.

In this study, the positions for the quantitative trait loci were identified based on the proportion of genetic variance explained by 5 consecutive SNP markers (sliding windows approach). Moreover, the sliding windows method with small window sizes (5 or 10 SNPs per window) identified the fewest false positives when compared to larger window sizes in simulation study (Beissinger et al., 2015). However, the best window size varies depending on the genetic background of the trait and the genotyping methods applied (Beissinger et al., 2015). Each window segment presents Manhattan plot results.

Gene search and identified QTL

Genome-wide association analyses for longevity and lifetime production traits were conducted with SNP effects. The SNPs within genomic windows that explained more than 1% of the proportion of the genetic variance were chosen as significant SNPs and evaluated to determine their suitability as possible candidate genes or quantitative trait loci (QTL). The significant SNPs within each QTL region were searched using the *Sus scrofa* Build 11.1 assembly and Ensembl Genome Browser (http://www.ensembl.org/Sus_scrofa/Info/Index). If no genes were within a genomic region, the flanking regions about 2.0 Mb around a significant SNP were considered to possibly represent the locus. Identifying the biological function for the candidate genes was obtained using GeneCards (https://www.genecards.org/). The Pig QTL database (http://www.animalgenome.org/cgi-bin/QTLdb/SS/index) was used to identify previous QTLs in the pig genome.

RESULTS

Descriptive statistics

Descriptive statistics for longevity and lifetime production trait for the Thai Landrace pig are summarized in Table 1. The mean age at first farrowing was 374 days. Thai Landrace sows remained in the sow herd for an average of 998 days and had 53.4 of piglets born alive during lifetime and weaned 48.6 piglets during their lifetime. Whereas, the mean lifetime weaning to first service interval was 27.7 days. The number of records, mean, minimum, maximum and standard deviation (SD) for the traits evaluated from the data set are presented in Table 1.

Table 1. Descriptive statistics for longevity and lifetime production traits from a Thai Landrace pig population.

Breed	Trait[1]	N	Mean	Minimum	Maximum	SD[2]
Landrace	AFF	12,843	374	289	460	31.5
	LPL	12,843	998	316	1861	350
	LNBA	12,843	53.4	0	129	26.9
	LNW	12,843	48.6	0	110	24.7
	LW2S	12,843	27.7	3	143	17.6
	LTP365	12,843	18.3	0.0	32.7	4.9

[1]AFF = age at first farrowing; LPL = length of productive life (interval from birthdate to last farrowing date); LNBA = lifetime number of piglets born alive; LNW = lifetime number of piglets weaned; LW2S = lifetime weaning to first service interval and LTP365 = lifetime pig efficiency was calculated as the lifetime pig production (the number of piglets born alive during a sow's lifetime) divided by the length of productive life × 365.[2]SD = standard deviation.

Heritability estimates and correlations among traits

Heritability estimates (±SE) are presented in Table 2 (diagonal elements). Heritability estimates (±SE) for longevity and lifetime production traits were 0.11 ± 0.02, 0.02 ± 0.01, 0.03 ± 0.01, 0.03 ± 0.01, 0.01 ± 0.01 and 0.06 ± 0.01 for AFF, LPL, LNBA, LNW, LW2S and LTP365, respectively. The heritability estimates obtained with genomic information for longevity and lifetime production traits were low. The low heritabilities for

longevity and lifetime production traits indicate that these traits should utilize genomic information in the genetic evaluation of the traits to enhance selection accuracy through genomic selection.

Table 2. Genetic (below diagonal) and phenotypic (above diagonal) correlations, heritabilities (diagonal) estimates and their standard error for longevity and lifetime production traits in a Thai Landrace pig population.

Trait[1]	AFF	LPL	LNBA	LNW	LW2S	LTP365
AFF	0.11 ± 0.02	-0.15 ± 0.01	-0.27 ± 0.01	-0.18 ± 0.01	-0.30 ± 0.01	-0.33 ± 0.00
LPL	0.00 ± 0.01	0.02 ± 0.01	0.85 ± 0.00	0.91 ± 0.01	0.44 ± 0.02	0.58 ± 0.01
LNBA	-0.08 ± 0.01	0.92 ± 0.00	0.03 ± 0.01	0.96 ± 0.00	0.42 ± 0.01	0.90 ± 0.00
LNW	-0.07 ± 0.01	0.92 ± 0.00	0.97 ± 0.00	0.03 ± 0.01	0.29 ± 0.01	0.80 ± 0.00
LW2S	-0.03 ± 0.01	0.64 ± 0.01	0.58 ± 0.01	0.57 ± 0.01	0.01 ± 0.01	0.29 ± 0.01
LTP365	-0.15 ± 0.01	0.67 ± 0.01	0.87 ± 0.00	0.81 ± 0.00	0.41 ± 0.01	0.06 ± 0.01

[1]AFF = age at first farrowing; LPL = length of productive life (interval from birthdate to last farrowing date); LNBA = lifetime number of piglets born alive; LNW = lifetime number of piglets weaned; LW2S = lifetime wean to first service interval and LTP365 = lifetime pig efficiency was calculated as the lifetime pig production (the number of piglets born alive during a sow's lifetime) divided by the length of productive life × 365.

The phenotypic and genetic correlations (±SE) are reported in Table 2. Estimated genetic correlations between AFF and LPL (-0.15 ± 0.10), LNBA (-0.27 ± 0.09), LNW (-0.18 ± 0.09), LW2S (-0.30 ± 0.12) and LTP365 (-0.33 ± 0.08) were generally moderate and negative. This suggests that selection for decreased age at first farrowing would improve lifetime productivity. Whereas, favorable genetic correlations between LPL and LNBA, LNW, LW2S and LTP365 were observed (0.85 ± 0.02, 0.91 ± 0.02, 0.44 ± 0.07 and 0.58 ± 0.08, respectively). These results indicate that selection for LPL may lead to desirable improvements in LNBA, LNW, LW2S and LTP365. Thus, selection for LPL could be included in the breeding program to improve overall sow productivity. Similarly, favorable moderate negative phenotypic correlations between AFF with LPL, LNBA, LNW, LW2S and LTP365 were found (0.00 ± 0.01, -0.08 ± 0.01, -0.07 ± 0.01, -0.03 ± 0.01 and -0.15 ± 0.01, respectively). The positive phenotypic correlations between LPL with LNBA, LNW, LW2S and LTP365 (0.92 ± 0.00, 0.92 ± 0.00, 0.64 ± 0.01 and 0.67 ± 0.01, respectively) were observed in the present study. This indicates that AFF would be positively affected when selecting to improve longevity and lifetime production traits.

GWAS for longevity and lifetime production traits

The GWAS results for longevity and lifetime production traits are shown in Table 3. Proportion of genetic variance explained by each window segments for longevity and lifetime production traits present Manhattan plot results (Figure 1, 2, 3, 4, 5 and 6). The 126 regions were detected on *Sus scrofa* chromosome (SSC) 1, 2, 4, 5, 7, 9, 11, 12 13, 14, 15 and X. A total of 50 different regions within genes and 27 candidate genes were found associated with all traits analyzed. The significant SNPs that explained greatest genetic variance for AFF, LPL, LNBA, LNW, LW2S and LTP365 were rs80823209 (SSC14: 1.76%), rs80883029 (SSCX: 1.74%), rs81473999 (SSCX: 2.59%), rs81473999 (SSCX: 2.67%), rs80826455 (SSC1: 2.21%) and rs81473999 (SSCX: 1.93%), respectively (Table 3). The relatively small fraction of the genetic variance explained indicates that both longevity and lifetime production traits are polygenic traits.

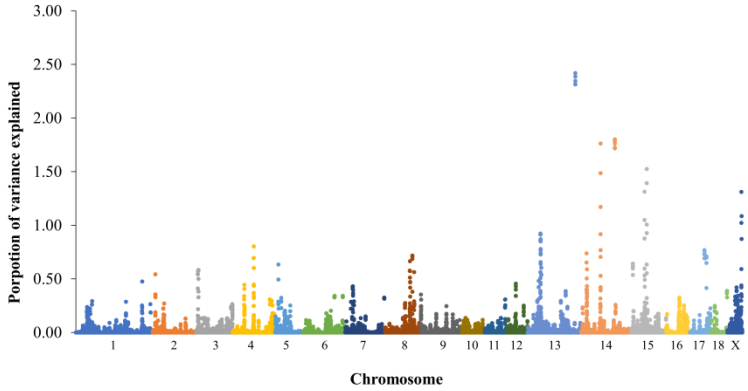

Figure 1. Manhattan plot of proportion of genetic variance explained by 5 consecutive SNP markers forage at first farrowing (AFF).

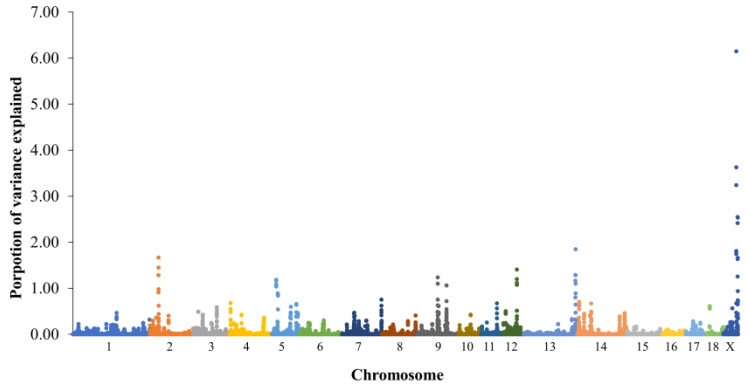

Figure 2. Manhattan plot of proportion of genetic variance explained by 5 consecutive SNP markers for length of productive life (LPL).

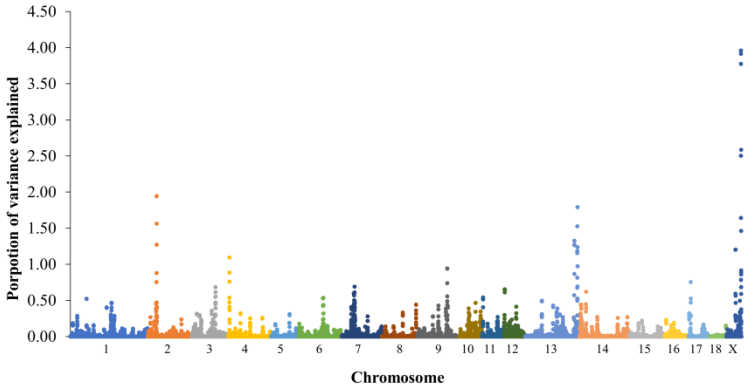

Figure 3. Manhattan plot of proportion of genetic variance explained by 5 consecutive SNP markers for lifetime number of piglets born alive (LNBA).

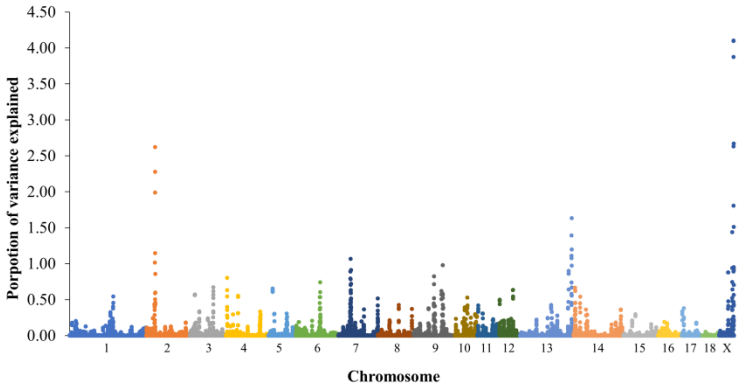

Figure 4. Manhattan plot of proportion of genetic variance explained by 5 consecutive SNP markers for lifetime number of piglets weaned (LNW).

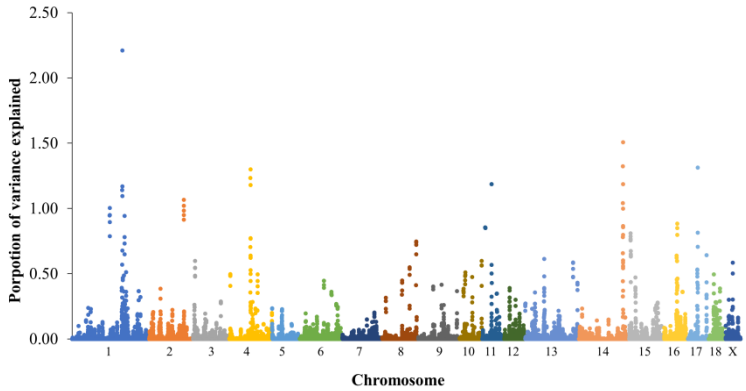

Figure 5. Manhattan plot of proportion of genetic variance explained by 5 consecutive SNP markers for lifetime wean to first service interval (LW2E).

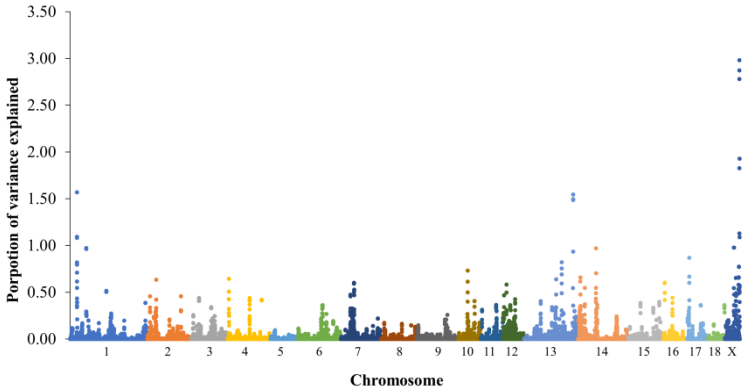

Figure 6. Manhattan plot of proportion of genetic variance explained by 5 consecutive SNP markers for lifetime pig efficiency (LTP365).

Regions or candidate genes associated with the traits analyzed in this study were identified. A total of 27 candidate genes, were identified as being associated with one or more the traits evaluated in the Landrace pig population in the present study (Table 3). The 5 candidate genes identified for AFF, located on SSC14 (*RYR2*), SSC15 (*HERC2* and *PLEKHA2*) and SSCX (*CD99L2* and *MTMR1*).

Table 3. Genes identified as impacting longevity and lifetime production traits based the proportion of variation > 1.0% explained by five consecutive SNP windows from a Thai Landrace pig population.

Trait[1]	SNP[2]	Chromosome	Candidate gene	Gene location (bp)	Proportion[3]
AFF	rs80823209	14	*RYR2*	53,653,486-54,194,883	1.76
	rs80985744	14	*RYR2*	53,653,486-54,194,883	1.49
	rs81453206	15	*HERC2*	56,437,557-56,649,117	1.39
	rs81473868	X	*MTMR1*	122,394,051-122,458,307	1.31
	rs80851694	14	*RYR2*	53,653,486-54,194,883	1.17
	rs81285190	X	*CD99L2*	122,454,381-122,535,992	1.09
	rs81452902	15	*PLEKHA2*	47,626,110-47,713,346	1.05
LPL	rs80883029	X	*ATP11C*	114,394,433-114,573,919	1.74
	rs81473999	X	*TMLHE*	125,598,100-125,673,686	1.66
	rs81442718	13	*KCNJ6*	201,230,226-201,525,964	1.29
	rs81328855	2	*PDHX*	26,015,857-26,094,846	1.28
	rs81442715	13	*KCNJ6*	201,230,226-201,525,964	1.16
	rs81477474	9	*SEMA3A*	96,066,121-96,385,049	1.06
	rs80863853	5	*BTBD11*	12,754,539-13,069,527	1.04
LNBA	rs81473999	X	*TMLHE*	125,598,100-125,673,686	2.59
	rs81442718	13	*KCNJ6*	201,230,226-201,525,964	1.53
	rs81474001	X	*ENSSSCG00000033936*	125,468,415-125,521,942	1.46
	rs81298710	13	*APP*	189,432,066-189,715,911	1.33
	rs81242095	13	*APP*	189,432,066-189,715,911	1.27
	rs81328855	3	*PDHX*	26,015,857-26,094,846	1.27
	rs81478500	13	*APP*	189,432,066-189,715,911	1.26
	rs81479523	X	*TSC22D3*	88,171,330-88,234,608	1.20
	rs81346820	X	*FRMPD3*	87,960,668-88,053,273	1.20
	rs81442715	13	*KCNJ6*	201,230,226-201,525,964	1.16
	rs81381462	4	*COL22A1*	4,169,200-4,313,245	1.10
LNW	rs81473999	X	*TMLHE*	125,600,312-125,673,666	2.67
	rs81328855	2	*PDHX*	26,015,857-26,094,846	1.99
	rs81474001	X	*ENSSSCG00000033936*	125,468,415-125,521,942	1.51
	rs81442718	13	*KCNJ6*	201,230,226-201,525,964	1.39
	rs81442715	13	*KCNJ6*	201,230,226-201,525,964	1.11
	rs80944747	7	*CMTR1*	33,000,553-33,063,383	1.07
LW2S	rs80826455	1	*ITGA11*	166,184,481-166,310,972	2.21
	rs80859099	14	*ATRNL1*	125,406,897-126,178,840	1.51
	rs320582474	14	*FAM160B1*	125,158,266-125,196,249	1.32
	rs80898068	17	*ATRN*	32,054,251-32,239,527	1.31
	rs80992126	14	*ATRNL1*	125,406,897-126,178,840	1.19
	rs80937006	4	*CHD7*	72,573,566-72,694,141	1.18
	rs80855587	1	*ITGA11*	166,184,481-166,310,972	1.17
	rs80891024	1	*ITGA11*	166,173,135-166,310,797	1.14
	rs80985275	1	*ITGA11*	166,173,135-166,310,797	1.09
	rs80952587	2	*ALDH7A1*	129,662,293-129,713,728	1.02
LW2S	rs80827731	1	*TCF4*	104,719,116-105,079,919	1.00
LTP365	rs81473999	19	*TMLHE*	125,598,100-125,673,686	1.93
	rs80935720	1	*RMND1*	14,794,909-14,851,848	1.57
	rs81298710	13	*APP*	189,432,066-189,715,911	1.55
	rs81242095	13	*APP*	189,432,066-189,715,911	1.50
	rs81478500	13	*APP*	189,432,066-189,715,911	1.48
	rs80787893	1	*ZBTB2*	14,866,060-14,894,954	1.09
	rs81474001	19	*ENSSSCG00000012811*	125,485,256-125,506,846	1.09
	rs345278935	1	*RMND1*	14,794,909-14,851,848	1.08

[1]AFF = age at first farrowing; LPL = length of productive life (interval from birthdate to last farrowing date); LNBA = lifetime number of piglets born alive; LNW = lifetime number of piglets weaned; LW2S = lifetime wean to first service interval and LTP365 = lifetime pig efficiency was calculated as the lifetime pig production (the number of piglets born alive during a sow's lifetime) divided by the length of productive life × 365. [2]SNP rsID. [3]The proportion of additive genetic variance explained by five consecutive SNP windows.

However, these candidate genes do not show relevance for other traits. Similarly, the four significant SNPs located within *ITGA11* (SSC1) were associated with LW2S. Although several QLT regions that were associated with LW2S were observed, these

regions were located on SSC1 at *TCF4* gene, SSC2 at *ALDH7A1* gene, SSC4 at *CHD7* gene, SSC14 at *ATRNL1* and *FAM160B1* gene and SSC17 at *ATRN* gene, but these genes were not found to be associated with other traits. The two significant SNPs were within the genes, rs80883029 (SSCX: 114.44 Mb) located at *ATP11C* (114.39-114.57 Mb) was associated with LPL and rs81473999 (SSCX: 125.66 Mb) within the *TMLHE* gene (125.59-125.67 Mb) was associated with LNBA, LNW and LTP365. Moreover, candidate genes that were associated with more than one trait were observed. For example, *PDHX* (SSC3) and *KCNJ6* (SSC13) showed a strong association with LPL, LNBA and LNW. *TMLHE* was an especially interesting gene that showed associations with more than one trait (LPL, LNBA, LNW and LPT365). Additionally, the *APP* (SSC13) gene was associated with LNBA and LTP365.

DISCUSSION

Current results show that the heritability estimates for AFF, LPL, LNBA, LNW, LW2S and LTP365 were low. According to previously reported findings, the heritability estimates for LPL ranged between 0.08 to 0.22 for LR sows (Sevón-Aimonen and Uimari, 2013). Similarly, results from other breeds or crossbred females reported low heritability estimates for LPL (Noppibool et al., 2016). Whereas, AFF has been reported to be genetically favorably associated with LPL, our findings indicated that selection to reduce AFF would improve longevity traits. These findings agree with those of Serenius and Stalder (2007), who reported that gilts that farrowed their first litter at an earlier age are more likely to stay in the herd longer and produce more piglets in a lifetime. Moreover, sows with older AFF would have increased culling risk (Serenius and Stalder, 2007). Accordingly, in our study, relatively high genetic correlations between LPL and LNBA, LNW were found (0.85 ± 0.00 and 0.91 ± 0.01, respectively). Previously literature indicated that sow longevity (LPL) is moderately associated with number of piglets weaned (Serenius et al., 2008). It was concluded that selection for LPL was not antagonistic with AFF and lifetime production. Estimated genetic correlations between LPL and LNBA, LNW, LW2S and LTP365 were positive and moderate to high (Table 2). Furthermore, selection for AFF could improve lifetime production traits in the Thai Landrace pig population. A low heritability for LPL, LNBA, LNW, LW2S and LTP365 was observed in our study. However, it is likely that it is still possible to improve longevity and lifetime production traits by implementing a genomic selection program.

We found that most of the SNPs are located in intergenic regions between coding genes. Moreover, we observed 50 regions within 27 candidate genes that were associated with all traits evaluated in our study. However, other potentially relevant regions associated with LPL, LNBA, LNW and LTP365 were identified. For example, the regions at the *APP*, *KCNJ6*, *TMLHE* and *PDHX* genes appear to be important. Especially, the six SNPs in the *KCNJ6* gene that were observed to be significantly associated with LPL, LNBA and LNW in our study. These SNPs are members of the G protein-coupled inwardly-rectifying potassium (GIRK) channel gene, which may be involved in regulating insulin secretion by glucose and/or neurotransmitters acting through G-protein-coupled receptors. In animals, *KCNJ6* (GIRK2) genes may influence responses to pain and opioid analgesics (Ikeda et al., 2000). Furthermore, the *TMLHE* gene was observed to be associated with more than one trait (LPL, LNBA, LNW and LPT365) in our study. The *TMLHE* gene is involved with

carnitine synthesis in the liver. Musser et al. (1999) reported that supplementing carnitine to sows during gestation, lactation, or both increased the number of pigs born alive. The effect of carnitine was through its action on insulin like growth factor 1 secretion, which improves intrauterine fetal nutrition (Rosenbaum et al., 2013). However, Onteru et al. (2011) reportedthat the *SLC22A18* gene on SSC2 was associated with lifetime total number born and that it may play a role in reproductive tissues and contribute to reproductive processes, which differs from our findings concerning the *TMLHE* gene on SSCX. This gene is involved in carnitine synthesis in the liver in the sow during gestation while the gene *SLC22A18* on SSC2 is expressed in the placenta and plays a role in reduced fetal intrauterine growth.

The candidate genes that affect AFF identified in our study were located on SSC14, SSC15 and SSCX including several genes: *RYR2*, *PLEKHA2*, *HERC2*, *MTMR1* and *CD99L2*. Moreover, we identified three SNP regions located within *RYR2* that are associated with cardiac diseases (Peng et al., 2016). In the pig, the *RYR1* gene has been found to be associated with several diseases, such as malignant hyperthermia (MH) (Fujii et al., 1991) and central core disease (CCD) (Robinson et al., 2006). In contrary, Nonneman et al. (2014) reported that the most regions associated with failure to attain puberty were on observed to be located on SSC4 and enclosed the *NHLH2* gene. The deletion of the *NHLH2* gene in female mice has been shown to result in delayed puberty and shorter reproductive lifespan (Johnson et al., 2004). In addition, the regions associated with LW2S were detected, rs80826455, rs80855587, rs80891024 and rs80985275 and they were within the *ITGA11* gene on SSC1. The *ITGA11* gene is a collagen receptor which is expressed in a subset of mesenchymally-derived tissues during embryogenesis (Zhang et al., 2002). Although several QTL regions were found in this study, many of these QTL were located in intergenic regions. The results from the present study indicate that longevity and lifetime production traits are complex polygenic traits in pigs.

The results from our study showed that genetic parameters could be estimated with genomic information and the heritability estimates for longevity and lifetime production traits were low. Moreover, LPL was favorably associated with lifetime production traits. Thus, selecting to improve LPL would have a tendency to improve lifetime prolificacy and reduce AFF. though it would not affect lifetime production traits. Our findings provided a candidate gene list for sow longevity and lifetime production traits estimated using a whole genome association study. Incorporating ssGBLUP and markers from ssGWAS into a maternal line swine-breeding program could be used to improve selection accuracy and the genetic improvement rate for sow longevity and other lifetime production traits.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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