

## Empirical Bayes factor analyses of quantitative trait loci for gestation length in Iberian × Meishan F<sub>2</sub> sows

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*The aim of this study was to investigate chromosomal regions affecting gestation length in sows. An experimental F<sub>2</sub> cross between Iberian and Meishan pig breeds was used for this purpose and we genotyped 119 markers covering the 18 porcine autosomal chromosomes. Within this context, we have developed a new empirical Bayes factor (BF) approach to compare between nested models, with and without the quantitative trait loci (QTL) effect, and after including the location of the QTL as an unknown parameter in the model. This empirical BF can be easily calculated from the output of a Markov chain Monte Carlo sampling by averaging conditional densities at the null QTL effects. Linkage analyses were performed in each chromosome using an animal model to account for infinitesimal genetic effects. Initially, three QTL were detected at chromosomes 6, 8 and 11 although, after correcting for multiple testing, only the additive QTL located in cM 110 of chromosome 8 remained. For this QTL, the allelic effect of substitution of the Iberian allele increased gestation length in 0.521 days, with a highest posterior density region at 95% ranged between 0.121 and 0.972 days. Although future studies are necessary to confirm if detected QTL is relevant and segregating in commercial pig populations, a hot-spot on the genetic regulation of gestation length in pigs seems to be located in chromosome 8.*

**Keywords:** Bayes factor, gestation length, pigs, quantitative trait loci

### Introduction

The moderate to high values of heritability estimated for gestation length during last decade (Hananberg *et al.*, 2001; Serenius *et al.*, 2004; Nguyen *et al.*, 2006) have increased its importance as a potential breeding goal to improve the efficiency of the sow per time unit. On the other hand, an increase in gestation length has been related with an improved piglet vitality at birth and the reduced stillbirths (Zaleski and Hacker, 1993; Leenhouders *et al.*, 1999; Knol *et al.*, 2002). There is substantial controversy on the relation between gestation length and incidence of splay leg piglets (Sellier and Ollivier, 1982; Van der Heyde *et al.*, 1989), and the reduction of gestation length has been related with an increase of the farrowing duration (Van der Heyde *et al.*, 1989). As a whole, gestation length could be viewed as a useful indicator of piglet viability and plays an important role in pig reproduction. Given the substantial relation between gestation length and piglet viability and survival, it is interesting to improve our

knowledge about its genetic background and to evaluate the benefit of marker-related strategies of selection.

Genome scans for quantitative trait loci (QTL) in F<sub>2</sub> crosses exploit the genetic divergence between two breeds to detect chromosomal regions linked to traits of interest. Within this context, we generated an Iberian × Meishan F<sub>2</sub> intercross, an important genetic resource for QTL detection because both breeds were produced from independent domestication processes. Indeed, there is substantial evidence that the Iberian breed has not been introgressed with Asian alleles (Alves *et al.*, 2003), a current influence in the greater part of the European breeds (Haley and Lee, 1993). Within this context, the aim of our research was to perform a genome scan to detect QTL related with gestation length in order to go deeply in the knowledge of the genetic basis of this trait.

### Material and methods

#### *Experimental data source*

Data on gestation length were obtained from an F<sub>2</sub> experimental design for detecting QTL for reproductive

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**Table 1** Summary of the gestation length data set

	<i>n</i>	$\bar{x}$	s.e.
Overall	855	112.16	0.08
Reproductive cycle			
First	249	111.78	0.19
Second	224	112.03	0.12
Third	202	112.36	0.17
Fourth	180	112.64	0.13
Litter size			
1 to 6 piglets	124	112.81	0.18
6 to 8 piglets	215	112.07	0.14
9 to 11 piglets	334	112.08	0.13
12 to 18 piglets	182	111.87	0.18
Year of parturition			
2002	45	111.38	0.20
2003	481	111.95	0.11
2004 and 2005	329	112.45	0.11

traits in pigs. A total of 855 records of gestation length from 249 Iberian  $\times$  Meishan  $F_2$  sows were recorded in Nova Genètica experimental farm of Solsona (Lleida, Spain) between October 2002 and January 2005 (Table 1). Those sows were generated from 97  $F_1$  gilts mated with 8  $F_1$  boars, and the  $F_0$  generation composed of 3 Guadyerbas Iberian boars (CIA El Dehesón del Encinar, Toledo, Spain) and 18 Meishan sows (INRA, GEPA experimental unit, Surgères, France).

Sows followed a standard management during the four reproductive cycles.  $F_2$  sows were mated by AI with semen of Large White boars, penned in standard gestation crates during pregnancy, and transferred to climate-controlled farrowing rooms (24°C) 10 days before parturition. After delivery, the length of the lactation period was 22 to 25 days. Feeding of sows was restricted during the gestation period (9.2 MJ net energy (NE), 13.5% crude protein (CP) and 0.48% lysine), and *ad libitum* during lactation (9.8 MJ of NE, 17.5% CP and 0.82% lysine).

### Genotyping

Genomic DNA of purebred  $F_0$  individuals,  $F_1$  reproducers and 249  $F_2$  sows was extracted from blood or tail tissue using standard protocols (Gentra Systems, Minneapolis, MN, USA). All the individuals were genotyped for 109 microsatellites and 10 single-nucleotide polymorphisms (SNPs; Table 2). The microsatellite PCR products were analysed with the Genescan 3.7 software (Applied Biosystems, Warrington, UK) in a capillary electrophoresis equipment with fluorescent detection (ABI PRISM 310 Genetic Analyser; Applied Biosystems, Foster City, CA, USA). The analysis of SNPs was performed by primer extension for the *DBH* (Tomás *et al.*, 2006b), *VCAM1* (Ramírez *et al.*, 2003), *BMP1B* (Tomás *et al.*, 2006a), *PRLR* (Tomás *et al.*, 2006c) and *MTNR1A* (Ramírez *et al.*, 2005) genes, and by PCR-restriction fragment length polymorphism (RFLP) for the *ESR*

**Table 2** Markers genotyped and position (cM) for each autosomal pig chromosome (Chr)

Chr	Marker	cM	Chr	Marker	cM	Chr	Marker	cM
1	SW1515	0.0	6	SW316	86.9	12	SW2494	16.1
1	ESR $\alpha$ 1	10.1	6	S0228	103.4	12	GH	45.5
1	CGA	49.6	6	SW1881	117.8	12	SW1307	49.2
1	S0113	75.7	6	LEPR	119.8	12	SW874	64.9
1	S0155	86.5	6	SW1328	151.4	12	SW1956	77.1
1	SW1828	117.0	6	SW2419	158.0	12	S0106	90.2
1	DBH	148.9	7	S0025	0.0	12	SWR1021	105.6
2	IGF2	0.0	7	TNFB	68.8	13	S0076	0.0
2	S0141	34.7	7	S0066	91.1	13	SWR1008	25.9
2	SW240	49.3	7	SW632	120.5	13	SW398	48.6
2	SW395	64.7	7	S0212	149.9	13	SW2440	69.4
2	S0226	75.5	7	S0101	158.7	13	SW769	84.5
2	S0378	94.2	8	SW2410	0.0	14	SW857	0.0
2	S0036	139.9	8	SWR1101	41.7	14	SW1125	18.8
3	SW72	0.0	8	S0017	72.6	14	SW210	37.2
3	S0206	16.0	8	S0225	91.2	14	S0007	49.6
3	S0164	32.9	8	SW61	112.3	14	SW1081	61.1
3	S0216	63.7	8	BMP1B	120.3	14	SW1557	81.1
3	S0002	87.8	9	SW983	0.0	14	SW2515	96.3
3	SW349	97.2	9	SW21	9.8	15	S0355	0.0
4	SW2404	0.0	9	SW911	34.9	15	SW919	10.2
4	S0301	24.4	9	SW2571	75.6	15	SW111	25.4
4	S0001	44.6	9	SW2093	109.7	15	S0149	50.4
4	SW839	60.2	9	SW2116	143.7	15	SW936	70.0
4	S0214	77.7	9	SW1349	162.1	15	SW1119	100.0
4	SW445	101.2	10	S0038	0.0	16	SW742	0.0
4	VCAM1	109.7	10	SW1894	24.8	16	PRLR	19.4
4	S0097	123.1	10	SW2195	40.1	16	SW403	26.7
5	SJ024	0.0	10	S0070	52.3	16	SW2517	56.5
5	SWR453	44.4	10	SW1991	65.9	16	S0061	84.7
5	SW2425	55.0	10	SW1626	93.7	17	SW24	0.0
5	S0005	71.0	10	SWR67	103.4	17	SW2142	14.6
5	SW1987	80.4	11	S0385	0.0	17	SW1920	30.7
5	IGF1	98.6	11	S0182	26.4	17	S0359	44.3
5	SW378	117.3	11	SW2008	37.8	17	SW2431	76.2
6	MC1R	0.0	11	S0071	56.1	18	SW1023	0.0
6	SW973	21.9	11	SW703	84.9	18	SW787	19.7
6	SW1057	47.1	11	SW2413	100.0	18	S0120	32.1
6	S0087	63.7	12	FASN	0.0	18	SWR414	53.6
6	LHBP2	77.5	12	SW2490	5.7			

(Short *et al.*, 1997), *GH* and *FASN* (Rodríguez *et al.*, 2005), *LHBP2* (Muñoz *et al.*, 2005) and *MC1R* (Kijas *et al.*, 1998) genes. Linkage analysis was carried out by using the CRIMAP 2.4 software (Green *et al.*, 1990). Markers provided coverage of the 18 autosomes, with an average marker interval of 17.4 cM (sex-averaged map distance).

### Trait and operational model

Gestation length was defined as the days from first fertile insemination to farrowing. Systematic effects considered were order of parity of the sow with four levels according to the four first parturitions, litter size including piglets born alive and stillbirths (categorized as <6, 6 to 8, 9 to 11 and >11 piglets), and year of farrowing (2002, 2003 and 2004).

Note that only two deliveries occurred in January 2005 and they were assigned to the preceding year (see Table 1 for an extensive summary of the data set). Additive and dominant effects of the QTL were modelled following Haley and Knott (1992). The probabilities of each QTL genotype at positions throughout the pig genome were calculated with the QTLexpress software (Haley and Knott, 1992). Two random sources of variation were included in the model, the permanent environmental and the additive genetic effect attributable to each sow.

#### Calculation of the empirical Bayes factor

Consider the following model with QTL effects (model QTL):

$$\mathbf{y} = \mathbf{X}_1\mathbf{b} + \mathbf{X}_\lambda\mathbf{q} + \mathbf{Z}_1\mathbf{p} + \mathbf{Z}_2\mathbf{a} + \mathbf{e},$$

where  $\mathbf{y}$  contains  $n$  phenotypic records,  $\mathbf{X}_1$ ,  $\mathbf{X}_\lambda$ ,  $\mathbf{Z}_1$  and  $\mathbf{Z}_2$  are the incidence matrices of systematic ( $\mathbf{b}$ ), QTL ( $\mathbf{q}$ ), permanent environmental ( $\mathbf{p}$ ) and additive genetic ( $\mathbf{a}$ ) effects, and  $\mathbf{e}$  is the vector of residuals. In order to reduce the number of tests performed, QTL location within chromosome ( $\lambda$ ) is included as an additional unknown parameter in our mixed model and thus, values in  $\mathbf{X}_\lambda$  depends on  $\lambda$ . Note that  $\mathbf{q}$  is a column vector composed by the additive ( $\alpha$ ) and dominant effect ( $\delta$ ) of the QTL ( $\mathbf{q}' = [\alpha \ \delta]$ ) at a given chromosomal location (by cM), and it reduces to a scalar element if  $\delta$  is not considered. Following a standard Bayesian development, the joint distribution of model QTL is

$$\begin{aligned} p_{QTL}(\mathbf{y}, \mathbf{b}, \mathbf{q}, \mathbf{p}, \mathbf{a}, \sigma_p^2, \sigma_a^2, \sigma_e^2, \lambda) &= p_{QTL}(\mathbf{y}|\mathbf{b}, \mathbf{q}, \mathbf{p}, \mathbf{a}, \sigma_e^2) \\ &\times p_{QTL}(\mathbf{b})p_{QTL}(\mathbf{q})p_{QTL}(\lambda)p_{QTL}(\mathbf{p}|\sigma_p^2) \\ &\times p_{QTL}(\mathbf{a}|\mathbf{A}, \sigma_a^2)p_{QTL}(\sigma_p^2)p_{QTL}(\sigma_a^2)p_{QTL}(\sigma_e^2), \end{aligned}$$

where  $\mathbf{A}$  is the numerator relationship matrix, and  $\sigma_p^2$ ,  $\sigma_a^2$  and  $\sigma_e^2$  are the permanent environmental, additive genetic and residual variances, respectively. The conditional distribution of  $\mathbf{y}$  is assumed to be normally distributed:

$$p_{QTL}(\mathbf{y}|\mathbf{b}, \mathbf{q}, \mathbf{p}, \mathbf{a}, \sigma_e^2) \sim N(\mathbf{X}_1\mathbf{b} + \mathbf{X}_\lambda\mathbf{q} + \mathbf{Z}_1\mathbf{p} + \mathbf{Z}_2\mathbf{a}, \mathbf{I}_e\sigma_e^2)$$

with  $\mathbf{I}_e$  being an identity matrix with dimension  $n \times n$ . Permanent environmental and additive genetic effects are assumed normally distributed ( $p_{QTL}(\mathbf{p}|\sigma_p^2) \sim N(\mathbf{0}, \mathbf{I}_p\sigma_p^2)$  and  $p_{QTL}(\mathbf{a}|\mathbf{A}, \sigma_a^2) \sim N(\mathbf{0}, \mathbf{A}\sigma_a^2)$ , respectively), and prior distributions for variance components and systematic effects are stated as inverted scaled  $\chi^2$  distributions and flat distributions, respectively (see Varona *et al.*, 2001). Within chromosome, the location of the QTL ( $\lambda$ ) is assumed by cM with an *a priori* uniform distribution:

$$p_{QTL}(\lambda) = \frac{1}{L} \quad \text{if } \lambda \in [0, L] \text{ and } 0 \text{ otherwise,}$$

where  $L$  is the length of the chromosome. Finally, our empirical Bayes factor (BF) deviates from the procedure of

Varona *et al.* (2001) in the prior distributions for QTL effects. They are assumed flat:

$$\begin{aligned} p_{QTL}(\alpha) &= \frac{1}{2k_\alpha} \quad \text{if } \alpha \in [-k_\alpha, k_\alpha] \text{ and } 0 \text{ otherwise,} \\ p_{QTL}(\delta) &= \frac{1}{2k_\delta} \quad \text{if } \delta \in [-k_\delta, k_\delta] \text{ and } 0 \text{ otherwise,} \end{aligned}$$

with  $k_\alpha$  and  $k_\delta$  being the maximum value of  $\alpha$  and  $\delta$ , defined as the extreme situation when all the phenotypic variance ( $\sigma_T^2$ ) of gestation length is accounted by  $\alpha$  or  $\delta$ . Following Falconer and Mackay (1996) and Spencer (2002),  $k_\alpha$  and  $k_\delta$  can be obtained as

$$k_\alpha = \frac{\sigma_T}{\sqrt{2\phi_1\phi_2}} \text{ and } k_\delta = \frac{\sigma_T}{2\phi_1\phi_2},$$

where  $\phi_1 = \phi_2 = 0.5$ , the expected frequency of both QTL alleles in an  $F_2$  population. As is mentioned in previous lines, preliminary information from gestation length data was required to construct  $p_{QTL}(\alpha)$  and  $p_{QTL}(\delta)$  and consequently, our model must be viewed as an empirical Bayesian model (Carlin and Louis, 1996). This provides appropriate bounds for  $\alpha$  and  $\delta$  within the parametric space, and allows for an easy construction of the BF as is described below.

The null-hypothesis model is the no-QTL model (model 0), with the following joint distribution of records and parameters:

$$\begin{aligned} p_0(\mathbf{y}, \mathbf{b}, \mathbf{p}, \mathbf{a}, \sigma_p^2, \sigma_a^2, \sigma_e^2) &= p_0(\mathbf{y}|\mathbf{b}, \mathbf{p}, \mathbf{a}, \sigma_e^2)p_0(\mathbf{b})p_0(\mathbf{p}|\sigma_p^2) \\ &\times p_0(\mathbf{a}|\mathbf{A}, \sigma_a^2)p_0(\sigma_p^2)p_0(\sigma_a^2)p_0(\sigma_e^2). \end{aligned}$$

We can assume that the likelihood of model 0 is

$$p_0(\mathbf{y}|\mathbf{b}, \mathbf{p}, \mathbf{a}, \sigma_e^2) \sim N(\mathbf{X}_1\mathbf{b} + \mathbf{Z}_1\mathbf{p} + \mathbf{Z}_2\mathbf{a}, \mathbf{I}_e\sigma_e^2),$$

and prior distributions for the remaining parameters are identical to the prior distributions of model QTL.

Following García-Cortés *et al.* (2001) and Varona *et al.* (2001), only the analysis with the complex model (model QTL) is required to calculate the empirical BF between model QTL and model 0 ( $\text{BF}_{QTL,0}$ ),

$$\text{BF}_{QTL,0} = \frac{p_{QTL}(\mathbf{q} = 0)}{p_{QTL}(\mathbf{q} = 0|\mathbf{y})},$$

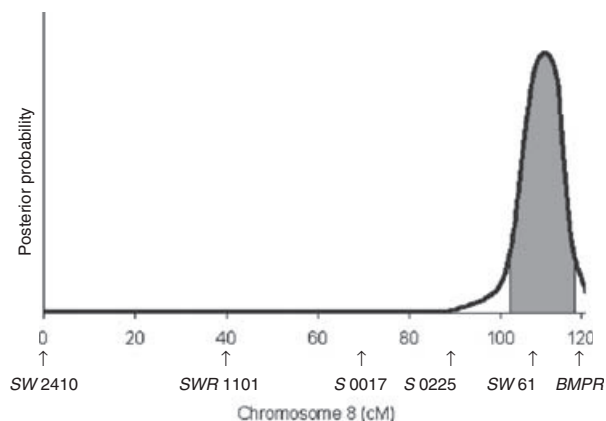
although additional assumptions are required to account for multiple testing (see Appendix). Note that  $p_{QTL}(\mathbf{q} = 0)$  equals to  $(4k_\alpha k_\delta)^{-1}$  for an additive and dominant QTL, whereas it reduces to  $(2k_\alpha)^{-1}$  if the dominance deviation is not accounted for. With the exception of  $\lambda$ , all parameters in model QTL were updated by Gibbs sampling (Gelfand and Smith, 1990). Following Varona *et al.* (2005), a Metropolis–Hastings step (Hastings, 1970) was used to obtain autocorrelated samples of  $\lambda$ , with a uniform proposal distribution centred at the current value of  $\lambda$  and covering 50 cM. It provided an acceptance rate greater than 20% in all chromosomes. The analyses were performed twice

at each chromosome, with  $\mathbf{q}$  defined as  $\mathbf{q}' = [\alpha \ 0]$  or  $\mathbf{q}' = [\alpha \ \delta]$  (see Appendix for a straightforward comparison between both models). For each analysis, five independent chains were launched with different starting value for  $\lambda$ . Each chain had a total of 500 000 iterations and the first 50 000 were discarded as burn-in (Raftery and Lewis, 1992). All correlated samples were used to calculate the posterior distributions using the ergodic property of the chain (Gilks *et al.*, 1996).

## Results and discussion

Taking García-Cortés *et al.* (2001) and Varona *et al.* (2001) as starting point, we developed an empirical new variant of the BF between nested models to detect QTL. This approach models QTL parameters as systematic effects with appropriate parametric bounds conditioned by the phenotypic variance. In general, BF methodology suffers from disadvantages due to its complexity of computation in complex models or its strong dependence on the assumed prior distributions (Kass and Raftery, 1995). Notwithstanding, the BF described by Varona *et al.* (2001) shows an important advantage in terms of dependence to the prior distributions for all parameters, with the only exception of the boundary variables, because they are the same in both competing models and then they are cancelled in the final calculation. In our case, prior distributions for QTL effects have been assumed flat within the rank of plausible values, with a low influence in posterior distributions.

Historically, the analyses of QTL have been stated as a typical example of multiple testing, increasing the probability of false-positives and unrealistic conclusions (Churchill and Doerge, 1994). Since a Bayesian point of view, numerous approaches have been proposed (Scott and Berger, 2003) although a key point in all cases is the number of tests carried out. The inclusion of  $\lambda$  (location of the QTL) as an unknown parameter in the model substantially reduces the number of independent tests performed in each chromosome. This approach allows for a straightforward detection of QTL within each chromosome, avoiding corrections for multiple testing if a single chromosome is analysed. If more than one QTL are located in the same chromosome, a multi-modal posterior distribution of  $\lambda$  is expected, and the empirical BF described above must be appropriately adapted to account for this peculiarity, e.g. reversible jump sampling (Stephens and Fisch, 1998). Nevertheless, only three chromosomes showed evidences of QTL affecting gestation length in our population and, all of them provided a unimodal posterior distribution of  $\lambda$  (see Figure 1 as example). A separate analysis by chromosome allows for faster mixing properties of the Monte Carlo Markov chain of  $\lambda$ , and still implies a huge reduction in multiple testing. Within this context, posterior odds can be viewed as a useful Bayesian tool to determine significant evidences depending on our *a priori* knowledge. It is not straightforward to define a standard prior odds as a general rule in QTL analyses, and appropriate prior odds must be



**Figure 1** Posterior density of quantitative trait loci (QTL) location in chromosome 8 (highest posterior density region at 95% is grey coloured).

defined in each case. Obviously, it implies a certain degree of arbitrariness, although several plausible values can be easily stated to verify the obtained results under a wider range of suitable scenarios.

Gestation length averaged 112.16 days ( $\pm 0.08$  days) in our  $F_2$  crossbred population (Table 1), a value smaller than the ones described in Asian pig breeds crossed with West-type breeds (113.0 to 113.7 days; Young, 1995 and 1998) as well as in West-type populations (113.5 to 114.5 days; Cassady *et al.*, 2002; Leenhouders *et al.*, 2003), and clearly shorter than the 116.1 days reported by Moeller *et al.* (2004). Modal estimates of variance components for gestation length were 0.67, 1.16 and 3.45 for additive genetic, permanent environmental and residual variances, respectively. Unfortunately, data from  $F_0$  generation were not available for the discrimination between additive variances from the parental populations and the segregation variance (Birchmeier *et al.*, 2002) and, in addition, genetic components related to dominance and linkage disequilibrium between loci can be absorbed by the additive genetic variance in an  $F_2$  design. Within this context, we must be cautious with the heritability provided by the current analysis ( $h^2=0.13$ ). This moderate value contrasts with the high heritabilities reported by Hanenberg *et al.* (2001) and Cassady *et al.* (2002), although it is similar to the one described by Nguyen *et al.* (2006).

The whole-genome scan suggested the presence of additive QTL affecting gestation length in pig chromosomes 6, 8 and 11 (Table 3). The additive QTL in chromosome 8 gave strong evidence following Jeffreys (1961;  $10 < \text{BF} \leq 31.62$ ) whereas QTL in chromosomes 6 and 11 did not worth more than a bare mention ( $1 < \text{BF} \leq 3.16$ ) (Table 3). The joint analysis of additive and dominant QTL effects reduced BF. The models with pure-additive QTL were preferable, with strong (chromosome 11), very strong (chromosome 6) and decisive (chromosome 8) evidences (Table 4). After correcting for multiple testing, posterior odds are shown in Table 5. They suggested that, although QTL in chromosomes 6 and 11 cannot be completely discarded under less-conservative prior odds, only the QTL in



**Table 3** Results of quantitative trait loci detection for gestation length

Chromosome	Position <sup>†</sup> (cM)	Bayes factor	QTL effects			
			Additive		Dominant	
			Mode	HPD95	Mode	HPD95
Model $\alpha^{\ddagger}$						
6	0	1.12	0.482	0.067 to 1.125		
8	110	25.33	-0.521	-0.972 to -0.121		
11	75	1.05	-0.505	-1.307 to -0.005		
Model $\alpha + \delta^{\S}$						
6	0	0.01	0.422	-0.118 to 1.128	0.017	-0.761 to 0.706
8	109	0.13	-0.581	-1.221 to -0.043	-0.104	-0.647 to 0.454
11	74	0.05	-0.590	-1.301 to 0.106	0.351	-0.553 to 1.066

<sup>†</sup>Mode.<sup>‡</sup>Model with additive quantitative trait loci (QTL) effect and without dominance deviation.<sup>§</sup>Model with additive and dominant QTL effects.**Table 4** Empirical Bayes factor between QTL with and without dominant effect

Chromosome	$BF_{QTL(\alpha),QTL(\alpha+\delta)}$	$BF_{QTL(\alpha+\delta),QTL(\alpha)}$
6	94.28	0.01
8	192.31	0.01
11	23.31	0.04

 $BF_{QTL(\alpha),QTL(\alpha+\delta)}$ : empirical Bayes factor (BF) of the quantitative trait loci (QTL) with additive effects against the QTL with additive and dominant effects. $BF_{QTL(\alpha+\delta),QTL(\alpha)}$ : empirical Bayes factor of the QTL with additive and dominant effects against the QTL with additive effects.

chromosome 8 must be quoted. The  $PO_{QTL,0}$  for this QTL reached higher than 1 estimates when the *a priori* expected number of QTL was 1 or greater, whereas QTL in chromosome 6 and 11 had posterior odds clearly lower or close to 1. The posterior odds draws a more stringent scenario under multiple testing and suggests that there is a QTL on gestation length in pig chromosome 8, it requiring future analyses to confirm its effects and magnitude.

A graphical representation of results for chromosome 8 is shown in Figure 1. The mode of the QTL location on chromosome 8 was placed at 110 cM, close to the marker SW61, with the highest posterior density region at 95% ranged between 103 and 118 cM (Figure 1). The joint analysis of additive and dominant effects reduced the empirical BF (Tables 3 and 4), with a slight change in the modal estimate of  $\lambda$  (109 cM). It can be related with a non-significant influence of the dominant deviation of the QTL, given that its higher posterior density at 95% included the null estimate (Table 3). Moreover, the empirical BF between the model with an additive QTL against the model with an additive and dominant QTL clearly favoured the first one, it being 193 times more probable (Table 4). Interestingly, the pig homologue of the Booroola fecundity gene (*BMPR1B*), previously related with gilt prolificacy at first parturition (Tomás *et al.*, 2006a), was located at the bound of that interval (118 cM), although it seems unlikely that *BMPR1B*

**Table 5** Posterior odds (additive quantitative trait loci (QTL) v. no-QTL) depending on the *a priori* expected number of QTL

Chromosome	Posterior odds				
	1 QTL	2 QTL	3 QTL	5 QTL	10 QTL
6	0.07	0.14	0.20	0.43	1.40
8	1.49	3.17	5.07	9.74	31.66
11	0.06	0.13	0.21	0.40	1.31

was the gene responsible for the gestation length QTL reported here. The additive fraction of the phenotypic variance explained by this QTL was around 3.4% (assuming modal estimates). No comparable QTL on gestation length have been mapped in chromosome 8, although QTL for closely related reproductive traits were detected in this chromosome (e.g. prenatal survival (King *et al.*, 2003); ovulation rate (Rathje *et al.*, 1997); uterine capacity (Rohrer *et al.*, 1999)). To the best of our knowledge, the previous research of Wilkie *et al.* (1999) in a Meishan  $\times$  Yorkshire cross described the first QTL for gestation length in chromosome 9. Our results did not allow confirmation of this QTL because significant results were not observed in this chromosome. Nevertheless, these differences could be due to the different breeds used in each  $F_2$  cross.

### Conclusion

The genetic basis of the main components of gestation length in sow has been investigated in an experimental Iberian  $\times$  Meishan  $F_2$  intercross. An empirical BF has been developed to scan QTL and it provided evidences of a QTL in chromosome 8, with an additive effect favourable to the Meishan allele of approximately half a day.

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## References

Alves E, Óvilo C, Rodríguez C and Silió L 2003. Mitochondrial DNA sequence variation and phylogenetic relationships of Iberian pigs and other domestic and wild pig populations. *Animal Genetics* 34, 319–324.

Birchmeier AN, Cantet RJC, Fernando RL, Morris CA, Holgado F, Jara A and Santos-Cristal MG 2002. Estimation of segregation variance for birth weight in beef cattle. *Livestock Production Science* 76, 27–35.

Carlin BP and Louis TA 1996. Bayes and empirical Bayes methods for data analysis. Chapman and Hall, New York, NY.

Cassady JP, Young LD and Leymaster KA 2002. Heterosis and recombination effects on pig reproductive traits. *Journal of Animal Science* 80, 2303–2315.

Churchill GA and Doerge RW 1994. Empirical threshold values for quantitative trait mapping. *Genetics* 138, 963–971.

Falconer DS and Mackay TFC 1996. Introduction to quantitative genetics. Longman, New York, NY.

García-Cortés LA, Cabrillo C, Moreno C and Varona L 2001. Hypothesis testing for the genetic background of quantitative traits. *Genetics Selection Evolution* 33, 3–16.

Gelfand A and Smith AFM 1990. Sampling based approaches to calculating marginal densities. *Journal of the American Statistical Association* 85, 398–409.

Gilks WR, Richardson S and Spiegelhalter DJ 1996. Markov chain Monte Carlo in practice. Chapman and Hall, London, UK.

Green P, Falls K and Crooks S 1990. Documentation of CRI-MAP version 2.4. Unpublished mimeo (available at <http://compgen.rutgers.edu/multimap/crimap>).

Haley CS and Knott SA 1992. A simple regression method for mapping quantitative trait loci in line crosses using flanking markers. *Heredity* 69, 315–324.

Haley CS and Lee GJ 1993. Genetic-basis of prolificacy in Meishan pigs. *Journal of Reproduction and Fertility* 48 (suppl), 247–259.

Hanenberg EHAT, Knol EF and Merks JWM 2001. Estimates of genetic parameters for reproduction traits at different parities in Dutch Landrace pigs. *Livestock Production Science* 69, 179–186.

Hastings WK 1970. Monte Carlo sampling methods using Markov chains and their application. *Biometrika* 57, 97–109.

Jeffreys H 1961. Theory of probability. Clarendon Press, Oxford, UK.

Kass RE and Raftery AE 1995. Bayes factors. *Journal of the American Statistical Association* 90, 773–795.

Kijas JMH, Wales R, Törnsten A, Chardon P, Moller M and Andersson L 1998. Melanocortin receptor 1 (MC1R) mutations and coat colour in pigs. *Genetics* 150, 1177–1185.

King AH, Jiang Z, Gibson JP, Haley CS and Archibald AL 2003. Mapping quantitative trait loci affecting female reproductive traits on porcine chromosome 8. *Biology of Reproduction* 68, 2172–2179.

Knol EF, Leenhouwers JI and Van der Lende T 2002. Genetic aspects of piglet survival. *Livestock Production Science* 78, 47–55.

Leenhouwers JI, Van der Lende T and Knol EF 1999. Analysis of stillbirth in different lines of pig. *Livestock Production Science* 57, 243–253.

Leenhouwers JI, Wissink P, Van der Lende T, Paridaans H and Knol EF 2003. Stillbirth in the pig in relation to genetic merit for farrowing survival. *Journal of Animal Science* 81, 2419–2424.

Moeller SJ, Goodwin RN, Johnson RK, Mabry JW, Baas TJ and Robinson OW 2004. The National Pork Producers Council Maternal Line National Genetic

Evaluation Program: a comparison of six maternal genetic lines for female productivity measures over four parities. *Journal of Animal Science* 82, 41–53.

Muñoz G, Fernández A, Barragán C, Silió L, Óvilo C and Rodríguez C 2005. SNP detection on LHB gene and association analysis with litter size in pigs. Proceedings of the 56th Annual Meeting of the European Association for Animal Production, June 5–8, Uppsala, Sweden.

Nguyen NH, McPhee CP and Wade CM 2006. Genetic variation and responses in reproductive performance of sows in lines selected for growth rate under restricted feeding. *Animal Science* 82, 7–12.

Raftery AE and Lewis SM 1992. How many iterations in the Gibbs Sampler? In *Bayesian statistics IV* (ed. JM Bernardo, JO Berger, AP Dawid and AFM Smith), pp. 763–774. Oxford University Press, New York, NY.

Ramírez O, Blanch M, Amills M, Noguera JL and Sánchez A 2003. Polimorfismo del gen vascular-cell adhesion molecule 1 (VCAM1) porcino. *Jornadas sobre Producción Animal Información técnica Económica Agraria (serie Producción Animal)* 24, 447–449.

Ramírez O, Tomás A, Barragán C, Noguera JL, Amills M and Varona L 2005. Effects of the pig melatonin receptor 1A gene (MTNR1A) on litter size in an Iberian × Meishan F2 population. First European Congress on Pig Genomics, Lodi, Italy.

Rathje TA, Rohrer GA and Johnson RK 1997. Evidence for quantitative trait loci affecting ovulation rate in pigs. *Journal of Animal Science* 75, 1486–1494.

Rodríguez C, Tomás A, Alves E, Ramírez O, Arqué M, Muñoz G, Barragán C, Varona L, Silió L, Amills M and Noguera JL 2005. QTL mapping for teat number in an Iberian-by-Meishan pig intercross. *Animal Genetics* 36, 490–496.

Rohrer GA, Ford JJ, Wise TH, Vallet JL and Christenson RK 1999. Identification of quantitative trait loci affecting female reproductive traits in a multi-generation Meishan-White composite swine population. *Journal of Animal Science* 77, 1385–1391.

Scott JG and Berger J 2003. An exploration of aspects of Bayesian multiple testing. Technical report, Duke University, Durham, NC.

Sellier P and Ollivier L 1982. A genetic study of splayleg in the new-born piglet. I. Multifactorial model with on threshold. *Annales de Génétique et de Sélection Animale* 14, 77–92.

Serenius T, Sevón-Aimonen M-L, Kauser A, Mäntysaari EA and Mäki-Tanila A 2004. Selection potential of different prolificacy traits in the Finnish Landrace and Large White populations. *Acta Agriculturae Scandinavica, Section A – Animal Science* 54, 36–43.

Short TH, Rothschild MF, Southwood OI, McLaren DG, De Vries A, Van der Steen H, Eckardt GR, Tuggle CK, Helm J, Vaske DA, Mileham AJ and Plastow GS 1997. Effect of the estrogen receptor locus on reproduction and production traits in four commercial pig lines. *Journal of Animal Science* 75, 3138–3142.

Spencer HG 2002. The correlation between relatives on the supposition of genomic imprinting. *Genetics* 161, 411–417.

Stephens DA and Fisch RD 1998. Bayesian analysis of quantitative trait locus data using reversible jump Markov chain Monte Carlo. *Biometrics* 54, 1334–1347.

Tomás A, Casellas J, Ramírez O, Pérez-Enciso M, Rodríguez C, Noguera JL and Sánchez A 2006a. Polymorphisms of the porcine dopamine β-hydroxylase gene and their relation to reproduction and piglet survivability in an Iberian × Meishan F2 intercross. *Animal Genetics* 37, 279–282.

Tomás A, Casellas J, Ramírez O, Muñoz G, Noguera JL and Sánchez A 2006b. High amino acid variation in the intracellular domain of the pig prolactin receptor (PRLR) and its relation to ovulation rate and piglet survival traits. *Journal of Animal Science* 84, 1991–1998.

Tomás A, Frigo E, Casellas J, Ramírez O, Óvilo C, Noguera JL and Sánchez A 2006c. An association study between polymorphisms of the porcine bone morphogenetic protein receptor type 1β (BMPRI1B) and reproductive performance of Iberian × Meishan F2 sows. *Animal Genetics* 37, 297–298.

Van der Heyde H, De Mets JP, Porreya L, Henderickx H, Calus A, Bekaert H and Buysse F 1989. Influence of season, litter size, parity, gestation length, birth weight, sex and farrowing pen on frequency of congenital splayleg in piglets. *Livestock Production Science* 21, 143–155.

Varona L, García-Cortés LA and Pérez-Enciso M 2001. Bayes factors for detection of quantitative trait loci. *Genetics Selection Evolution* 33, 133–152.

Varona L, Gómez-Raya L, Rauw WM, Óvilo C, Clop A and Noguera JL 2005. The value of prior information for detection of QTL affecting longitudinal traits: an example using Von Bertalanffy growth function. *Journal of Animal Breeding and Genetics* 122, 37–48.

Wilkie PJ, Paszek AA, Beattie CW, Alexander LJ, Wheeler MB and Schook LB 1999. A genomic scan of porcine reproductive traits reveals possible quantitative trait loci (QTLs) for number of corpora lutea. *Mammalian Genome* 10, 573–578.

Young LD 1995. Reproduction of F1 Meishan, Fengjing, Minzhu and Duroc gilts and sows. *Journal of Animal Science* 73, 711–721.

Young LD 1998. Reproduction of 3/4 White composite and 1/4 Duroc, 1/4 Meishan, 1/4 Fengjing, or 1/4 Minzhu gilts and sows. *Journal of Animal Science* 76, 1559–1567.

Zaleski HM and Hacker RR 1993. Effect of oxygen and neostigmine on stillbirth and pig viability. *Journal of Animal Science* 71, 298–305.

## Appendix

### *Comparison between pure-additive QTL and additive and dominant QTL*

Take  $BF_{QTL(\alpha),0}$  as the empirical Bayes factor (BF) between a pure-additive QTL model ( $QTL(\alpha)$ ) and the no-QTL model (Model 0), and  $BF_{QTL(\alpha+\delta),0}$  as the empirical BF between an additive and dominant QTL model ( $QTL(\alpha + \delta)$ ) and the no-QTL model. Note that both  $QTL(\alpha)$  and  $QTL(\alpha + \delta)$  are contrasted against model 0 and then, the empirical BF between the additive QTL and the additive and dominant QTL can be easily obtained as

$$BF_{QTL(\alpha),QTL(\alpha+\delta)} = \frac{BF_{QTL(\alpha),0}}{BF_{QTL(\alpha+\delta),0}}.$$

### *Correction for multiple testing*

From the standard definition of BF (Kass and Raftery, 1995):

$$PO_{QTL,0} = BF_{QTL,0} \times PrO_{QTL,0} = BF_{QTL,0} \times \frac{p_{QTL}}{p_0},$$

where  $PO_{QTL,0}$  is the posterior odds between model QTL and model 0 and  $PrO_{QTL,0}$  is the prior odds.  $PO_{QTL,0}$  can be viewed as a weighted BF accounting for a more realistic *a priori* probability for both models under multiple testing. We could assume that the *a priori* probability of both model QTL and model 0 could be appropriately defined depending on our degree of belief on the expected number of QTL before the analysis. In the standard development of the empirical BF described above, we assumed that the prior odds were 1 and the *a priori* probability for the QTL model and the no-QTL model were both 0.5 at each chromosome, providing an *a priori* expected number of QTL of 9. Obviously, it is an unrealistic assumption and a more-conservative criterion must be taken. If we initially expect  $n$  QTL, the *a priori* probability of the QTL model ( $p_{QTL}$ ) and the no-QTL model ( $p_0$ ) at each chromosome becomes  $n/18$  and  $(18 - n)/18$ , respectively. Posterior odds can be easily obtained as

$$PO_{QTL,0} = BF_{QTL,0} \times \frac{n}{18 - n},$$

which provides a straightforward correction for multiple testing.