Multivariate models applied to QTL detection for carcass composition on SSC7

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Linked and pleiotropic QTL influencing carcass composition traits detected on porcine chromosome seven.

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Summary

A multivariate QTL detection was carried out on fatness and carcass composition traits on SSC7. Single trait QTL have already been detected in the SLA region, and multivariate approaches have been used to exploit the correlations between the traits to obtain more information on their pattern: almost 500 measurements were recorded for backfat thickness (BFT1, BFT2), backfat weight (BFW) and leaf fat weight (LFW) but only half for intramuscular fat content (IMF), affecting the detection. First, groups of traits were selected using a backward selection procedure: traits were selected based on their contribution to the linear combination of traits discriminating the putative QTL haplotypes. Three groups of traits could be distinguished based on successive discriminant analyses: external fat (BFT1, BFT2), internal fat (LFW, IMF), and BFW. At least four regions were distinguished, preferentially affecting one or the other group, with the SLA region always influencing all the traits. Meishan alleles decreased all trait values but IMF, confirming an opportunity for marker assisted selection to improve meat quality with maintenance of carcass composition based on Meishan alleles.

1) INTRODUCTION

QTL have been detected for most major pig traits over the last decade (PigQTLDB, Hu et al., 2005). Increasing the frequency of favourable QTL alleles through marker assisted selection (MAS) may be very helpful to improve the efficiency of breeding schemes by reducing testing costs and increasing selection accuracy, especially when traits are difficult to measure, either because of the moment of the measure (late in animal life or after slaughtering) or because of their cost. Primary analyses are mostly based on single QTL single trait tests: as a result of a genome scan for correlated traits of interest, many QTL are often mapped for different traits with large confidence intervals in a given chromosomal region, possibly suggesting ghost QTL (Lander & Botstein, 1989). Difficulty of measurements and multiple QTL detections are both characteristics of mapping for carcass composition traits and intramuscular fat content (IMF) in the Swine Leukocyte Antigen (SLA) region on porcine chromosome seven (SSC7) (Bidanel & Rothschild, 2002). In such situations, implementing multivariate QTL detections, *i.e.* setting up models for multiple correlated traits and / or multiple linked locations, can improve power of detection and accuracy of localizations, and more precisely define the QTL pattern in that chromosomal region (Zeng, 1993; Zeng, 1994; Korol et al., 1995; Korol et al., 1998; Ronin et al., 1999; Kao et al., 1999; Korol et al., 2001; Nakamichi et al., 2001). In outbred designs, such strategies have long been limited due to high computing costs, but Gilbert & Le Roy (2007) proposed a multiple step strategy to efficiently pre-select traits to perform multidimensional mapping. In iterative steps, genetic linkage due to pleiotropic chromosomal regions was described by using linear combinations of traits to reduce model dimensions. Finally, multiple trait models including linked and single pleiotropic QTL were fitted and tested against each other. To illustrate the technique, this strategy was applied in a Large White x Meishan pig cross to fatness and carcass composition traits in the SLA region where QTL were already described (Bidanel et al., 2001; Bidanel et al., 2002; Milan et al., 2002). The four carcass fatness characteristics are routinely recorded and efficiently selected in French pig populations (see Tribout et al., 2004). The fifth trait, intramuscular fat content (IMF), is not measured in the selection schemes and was recorded on a limited number of progeny in the experimental cross. In this paper, the multivariate techniques were aimed at improving the data analysis of IMF by taking advantage of the correlations between the traits, and marginally at better localizing the loci and identifying pleiotropic effects.

2) MATERIAL AND METHODS

(i) Animals, traits and genotyping

The PORQTL project was a large program for QTL detection in Large White x Meishan F2 pigs carried out at INRA (Bidanel *et al.,* 2001). In this study, the following carcass composition traits were analyzed:

- two carcass cuts, *i.e.* backfat (backfat) and leaf fat (leaf fat) weights,

- two backfat thickness measured shortly after slaughter using a Fat-O-Meater probe between the 3rd and the 4th lumber vertebra at 8 cm from the spine (BFT1), and beneath the last rib at 6 cm from the mid-dorsal line (BFT2),

-intramuscular fat content (IMF) of the *Longissimus lumborum* muscle.

Phenotypic data were adjusted for systematic environmental effects (and slaughter weight for carcass cuts) as described in Milan *et al.* (2002). Further details on the measures can be found in Bidanel *et al.* (2001), Milan *et al.* (2002) and Bidanel *et al.* (2002).

Due to measurement costs, only a sub sample of 236 F2 males, offspring from 4 F1 boars and 16 F1 sows were measured for IMF within the PORQTL project, whereas almost 500 carcass adiposity measurements were available. In this study, all analyses were restricted to the sub sample in order to increase information on the IMF distribution among the progeny while not creating a missing data structure in multiple trait tests.

A total of 10 microsatellite markers were genotyped for all F0, F1 and F2 pigs as described in Bidanel *et al.* (2001). A multipoint linkage analysis was carried out for males, females and both sexes with the 2.4 version of the CriMap software (Green *et al.*, 1990) in order to calculate the genetic maps. The sex averaged map of SSC7 is presented in Figure 1.

(ii) QTL detection methods

The basis of the QTL detection technique in the QTLMAP software was described in Le Roy *et al.* (1998), Elsen *et al.* (1999), Goffinet *et al.* (1999) and Mangin *et al.* (1999) for usual single trait single QTL detections (ST). Interval mapping was used and a mixture of full- and half- sib families was assumed with no hypothesis about the number of QTL alleles and the allele frequencies within founder populations. In QTLMAP, test statistics were approximate likelihood ratio tests (LRT), retaining only the most probable sire haplotype and all dam phases with a probability higher than 0.1; the likelihood was linearised within full-sib families (Le Roy *et al.*, 1998). In practice all phases were built with certainty.

For the multivariate tests (Gilbert & Le Roy, 2007), we note M_p^q the model involving p traits and q QTL (p = 1 to 5 and q = 0 to 2 in this study). Note that the following holds:

- 2-QTL models M_p^2 represent a group of models where each QTL is pleiotropic on all p traits (for p>1)

- from M_p^1 to M_1^0 , nested models are obtained by removing traits from p to 1,

- from M_p^2 to M_p^0 , 1 pleiotropic QTL model M_p^1 is tested vs 2 pleiotropic linked QTL if M_p^1 is significant, else M_p^0 is used as the null hypothesis.

Multiple trait tests were based on two complementary approaches:

- a multivariate approach, where the joint influence on the traits was assumed to follow a multinormal distribution (MV under 1 QTL models (Gilbert & Le Roy, 2003), MV2 under 2 QTL models (Gilbert & Le Roy, 2007)),

- a univariate likelihood, where the joint influence was described using a linear combination of the traits. This linear combination was treated as a normally distributed new trait in QTL mapping models. At each position, 2 progeny groups were defined depending on the sire haplotype inherited at that position. A discriminant analysis was then applied to compute the linear combination of the traits which best discriminate the haplotypic progeny groups, *i.e.* which maximizes the ratio of the between group variability (variability due to the putative QTL at that position) and the within group variability (variability due to any other factor). Its computation was detailed in Gilbert & Le Roy (2003) for the no QTL, M_p^0, and the 1-QTL M_p^1 (DA) models, and in Gilbert & Le Roy (2007) for the 2-QTL models M_p^2, where both QTL can determine the traits (DA2).

Significance levels were estimated by Monte Carlo simulations, trait values being simulated with multinormal distributions (see Gilbert & Le Roy, 2003; Gilbert & Le Roy, 2007). When the null hypothesis was “no QTL”, independently of the genotypes, null means were simulated and variances corresponded to the known heritability of the traits. When the null hypothesis was “1 QTL”, first genotypes were simulated for markers together with a putative QTL located at the position of the maximum of the test statistic estimated under the corresponding M_k^1 model. Then, trait values were jointly simulated for the k traits under an additive multinormal model, conditional on the QTL genotype. The simulated QTL effects were equal to the effects estimated at the maximum of the test statistic obtained while testing the 1 QTL model for k traits with a MV test. Two thousand simulations were carried out for M_k^0 *vs* M_k^1 tests, but only 200 simulations could be performed for M_k^0 or M_k^1*vs* M_k^2 tests, due to excessive

computing times. Harrel and Davies (1982) approximations of the simulated distribution were applied to finally assess the thresholds. For single trait tests, the type-I errors a considered were systematically corrected to account for the number of traits k, using an approximated Bonferroni correction: for an expected $a_{expected}$ error, the test error a_{test} was $a_{test} = a_{expected} / k$.

(iii) Strategy for systematic analysis

The successive steps for multidimensional analyses were the following:

1) to test each trait separately for 0 QTL (M_1^0), 1 QTL (M_1^1), or 2 QTL (M_1^2) models,

2) to select the groups of traits jointly determined by the chromosomal region, with successive tests of M_k^0 *versus* M_k^1 , $k = p$ to *2* in a backward selection (see below),

3) to apply different genetic models for each group of traits so as to:

3.a) test a full 2 pleiotropic QTL model,

3.b) apply sub-models if necessary.

The 3 steps 1) to 3.a) could be run automatically, first using the single trait methods, *i.e.* ST for the single QTL tests (Le Roy et al., 1998), ST2 for the 2 QTL tests (Gilbert & Le Roy, 2007) and the DA technique to deal with the multiple trait selection of models. Tests of sub-models 3.b) were based on multivariate techniques and were hence time consuming. Only pertinent sub-models were pre-selected based on the M_1^2 and M_k^1 tests applied.

The backward selection of the traits in step 2 was performed using DA according to the following procedure:

2.a) An analysis with a $k=p$ trait model was performed,

2.b) When the test for 1 pleiotropic QTL was significant, the trait with the lowest contribution to the linear combination at the maximum of the test statistic was excluded,

2.c) An analysis with a k-1 trait model,

2.d) If the test with k-1 traits was at least as significant as the test with k traits, a new selection of traits following step 2.b) to 2.c) was run; when the test with k-1 traits was less significant than the test with k traits, the selection stopped and the model with k traits was considered as the most appropriate model.

After a first selection process from steps 2.a) to 2.d), a new analysis was carried out considering only the group of the removed traits, to have the opportunity to map a different genetic mechanism for this other group in the region.

3) RESULTS

(i) Single trait single QTL results

The results of M_1^0 *vs* M_1^1 tests for each trait (Table 1 and Figure 1) showed highly significant QTL in a 30 cM region in the SLA neighborhood for the 5 traits.

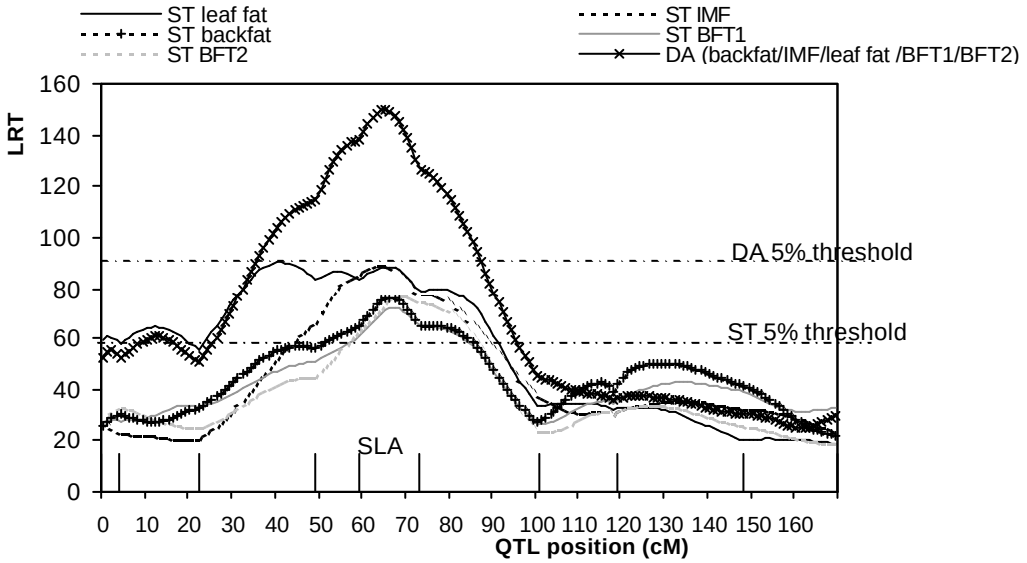

Figure 1: Likelihood ratio test on SSC7, single trait single QTL detection (ST) and 5-trait single QTL detection (DA). Arrows indicate marker positions. The 5% thresholds are the maximum 5% chromosome-wide thresholds among the studied traits.

Table 1: Single trait single QTL analysis: value, position and QTL allele substitution effects at the maximum of the test.

	backfat	IMF	leaf fat	BFT1	BFT2
MaxLRT	76.1	89.1	90.3	71.8	76.5
Position (cM)	66	64	41	67	69
Threshold (CW 5%) [A]	58.00	51.63	49.96	51.70	51.70
	Effects (σ_p units) [B]				
Sire 1	-0.56	1.20	-0.87	-0.70	-0.61
Sire 2	-0.48	0.91	-0.29	-0.48	-0.43
Sire 3	-0.56	0.78	-0.89	-0.46	-0.61
Sire 4	-0.72	0.39	-1.15	-0.65	-0.54
average	-0.58	0.83	-0.80	-0.57	-0.55

[A] CW = chromosome-wide; [B] Allele substitution effects (Meishan - Large White), σ_p = phenotypic standard deviation

The estimated substitution effects were large and similar for the 4 sires. Meishan alleles increased IMF, but decreased BFT1, BFT2, leaf fat and backfat, in accordance with the correlations between the traits corrected for environmental effects (Table 2). The high and positive correlations between carcass measurements followed expectation but the low negative correlations with IMF were the contrary to the literature parameters (Sellier, 1998), and may suggest the segregation of major cryptic alleles in the specific population studied.

Table 2: Phenotypic variance and phenotypic correlations.

Trait	backfat (kg)	IMF (%)	leaf fat (kg)	BFT1 (mm)	BFT2 (mm)
Mean	7.17	1.98	0.96	34.7	31.2
Variance	0.43	0.16	0.04	15.6	14.9
Correlations					
IMF	-0.15				
leaf fat	0.69	-0.17			
BFT1	0.87	-0.15	0.64		
BFT2	0.83	-0.23	0.66	0.85	

(ii) Single trait linked QTL analyses

Only leaf fat analysis showed significant maximum test statistic at the 5% chromosome-wide level (Figure 2) for linked QTL tests. The most likely positions for the QTL were 1 and 67 cM, with average effects of -0.26 s_p (phenotypic standard deviation) and -0.57 s_p for the first and second positions, respectively. The maximum likelihood for the 1 QTL model M_1^1 was highly significant at 41 cM with an estimate of -0.80 s_p for the average QTL effect. It could thus be interpreted as an evidence for a "ghost QTL" as described by Martinez & Curnow (1992).

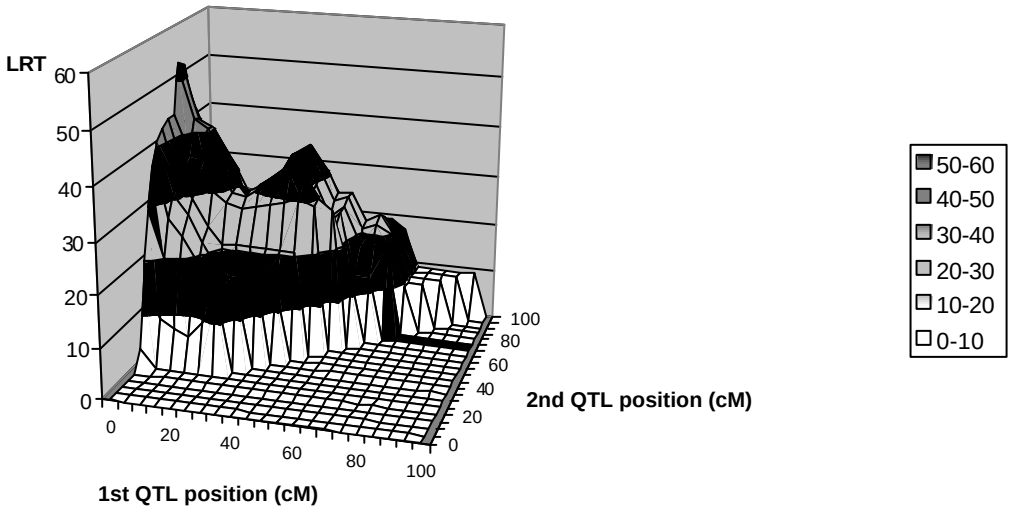

Figure 2 : Two-QTL grid-search for leaf fat: test statistic profile, detail from position 0 to 100 cM.

(iii) Multiple trait single QTL analyses

The results for the test of M_5^0 versus M_5^1 with MV and DA (Table 3 and Figure 1) showed strong evidence for a pleiotropic chromosomal region, with a maximum test statistic located around 64 cM. Average effects estimated with MV were very similar to those separately estimated under M_1^1. The residual correlation matrix – beside the QTL - estimated for that model was all positive but the correlation between IMF and BFT1 (-0.07), the remaining correlations with IMF ranging from 0.01 to 0.08.

(iv) Selection of groups of traits by single QTL analyses

Table 3 : Joint analysis of the five traits using a multivariate likelihood (MV) and a discriminant variable (DA), and successive selection of traits with DA.

	MV	DA			
Number of traits	5	5	4	3	2
MaxLRT	249.0	149.8	149.8	149.9	146.9
Position (cM)	64	65	65	65	65
Threshold (CW 5%) [A]	197.1	87.4			
Traits	Effects (σ_p units) [B]	Trait weights			
IMF	0.84	-0.72	-0.72	-0.71	-0.72
BFT1	-0.60	0.20	0.20	0.14	
BFT2	-0.61	-0.09	-0.09		
backfat	-0.59	-0.01			
leaf fat	-0.74	0.68	0.68	0.66	0.75

[A] CW = chromosome-wide; [B] Allele substitution effects (Meishan - Large White), σ_p = phenotypic standard deviation

From the M_5^1 model a selection of significant traits was applied as described previously (Table 3). Excluding first backfat, which only contributed for 0.36% to the linear combination, the test statistic with 4 traits remained the same and the likelihood profile was identical. The two backfat thicknesses were similarly removed from the joint analysis with no major change in the results so the final model retained only IMF and leaf fat, which equally contributed to the linear combination. The general likelihood profile along the linkage group remained very similar during the selection process (not shown). The QTL effects and the correlation between the traits beside the QTL influence for M_2^1 were estimated with the MV multivariate technique at the position of the maximum of the test statistic (65 cM): the average estimated substitution effects were 0.83 s_p for IMF and -0.75 s_p for leaf fat, so this locus induced a genetic correlation between IMF and leaf fat in contrast with the literature but in accordance with Table 1. The residual correlation beside the QTL was estimated to 0.05.

The 3 traits excluded BFT1, BFT2 and backfat were jointly analyzed with DA (Table 4). The analysis was significant at a 1% type-I level, and remained as significant removing backfat from the test. The average substitution effects were 0.57 s_p and 0.59 s_p, respectively, for BFT1 and BFT2, with a residual correlation (0.81) similar to their phenotypic correlation.

Table 4 : Trait selection using DA, for BFT1, BFT2 and BWT.

Number of traits	3	2
MaxLRT	82.1	80.1
Position	68	68
CW 1% threshold [A]	70.3	70
Traits	Trait weights	
BFT1	0.31	0.40
BFT2	0.51	0.68
backfat	0.27	

[A] CW = chromosome-wide

Based on these analyses, we distinguished three groups of traits referring to potentially different genetic patterns in this chromosomal region: 1) IMF + leaf fat, 2) BFT1 + BFT2, and 3) backfat. From that point, pleiotropic regions were tested for the segregation of pleiotropic linked QTL (M_2^1 *vs* M_2^2) using DA2.

(v) IMF and Leaf fat

With IMF and leaf fat, the DA2 test statistic was maximized for the couple of positions 0 and 66 cM, with a value of 91.5, significant at the 1% chromosome-wide level. Sub models of M_2^2 where the 2 QTL are not pleiotropic were then tested. A first model with 2 non pleiotropic QTL was rejected in comparison with the model with 2 pleiotropic QTL. Then, a new model, combining one QTL affecting only leaf fat and one pleiotropic QTL for IMF and leaf fat was tested in comparison with the following: 1) a single pleiotropic QTL model M_2^1 (where the new model was the alternative hypothesis); 2) a 2 pleiotropic QTL model (where the new model was the null hypothesis). M_2^1 was rejected at the 1% level, whereas the second model could not be rejected. Using MV2 to estimate the

corresponding effects and residual correlation, we finally retained a model with two QTL, the first one at 0 cM with an effect of -0.22 s_p on leaf fat, and the second one at 66 cM, with pleiotropic effects of -0.59 s_p and 0.83 s_p on leaf fat and IMF, respectively. This was highly consistent with the single trait results. The residual correlation was -0.19, close to the phenotypic correlation for these data.

(vi) BFT1 and BFT2

For BFT1 and BFT2, the DA2 maximum (positions 69 and 140 cM) was slightly below the 5% threshold. Conversely, the tests with MV2 were highly significant (74.4, the threshold for a 0.01 type-I error being 63.7) with most likely positions at 40 and 70 cM and estimated effects of -0.27 s_p and -0.32 s_p for BFT1, and -0.28 s_p and -0.38 s_p for BFT2, respectively. This difference suggests that at least 2 (at positions 40 and 70 cM) or 3 loci (with an additional position at 140 cM suggested by the LRT profiles for BFT1 and BFT2 in Figure 1) were dinfluencing these traits, with complex interactions that can not be handled in the current models (Gilbert et Le Roy, 2007). The residual correlation (0.85) remained unchanged compared to previous tests.

(vii) Joint analysis of the two groups of traits

A last test was conducted to compare the hypothesis of two pleiotropic QTL, each influencing one of the groups of traits, *vs* the hypothesis of one pleiotropic QTL determining the four traits. The maximum of the test statistic was very close to zero for adjacent positions around 70 cM and thus was not significant. For this region and until additional markers and recombination events are available, we thus can not conclude that different loci are actually segregating.

4) DISCUSSION AND CONCLUSION

This paper is an application of the methodology presented in Gilbert & Le Roy (2003, 2004, 2007), with some additional sub-models used to increase the power of detection and the understanding of the genetic pattern of QTL influencing IMF, a major trait for meat quality but difficult to measure. The analysis concluded with a model (Figure 3) pointing out at least 2 additional regions compared to the single trait single QTL detections previously conducted, around 0 cM and 140 cM. Moreover, the QTL locations were clarified compared to our earlier studies, resolving a ghost QTL for leaf fat in two different locations and pointing out at least 2 locations for backfat thickness.

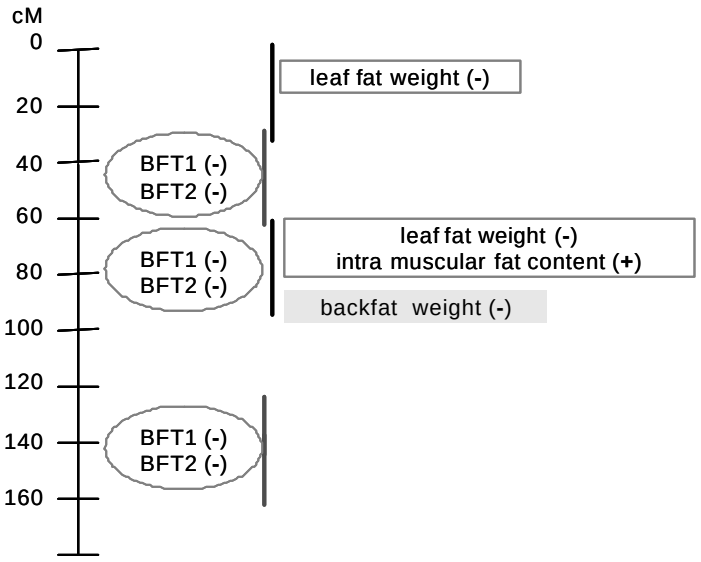

Figure 3: Summary of QTL model segregation for carcass composition on SSC7 using multidimensional models for detection. Four chromosomal regions, represented by vertical lines, were detected using three groups of traits distinguished by circles, rectangles or shaded rectangle.
(+) = increasing effect from Meishan alleles, (-) = increasing effect from Large White alleles.

Among QTL detection studies on the same data set, Quintanilla *et al.* (2002) conducted 2-QTL single trait tests. They found a significant result on SSC7, with two QTL located at positions 70 and 113 cM, affecting average daily gain between 3 and 10 weeks. On the contrary, they found no significant result for average backfat thickness during growth. The multiple trait approach used in the present study certainly helped reaching significance. Knott *et al.* (1998) detected linked QTL for the percentage of abdominal fat in a Wild Boar x Large White cross on SSC5 and X, but did not find anything on SSC 7. De Koning *et al.* (2000) also pointed out the possibility of QTL linkage for backfat thickness on SSC7.

Fixation of QTL alleles in grand-parental breeds was strongly suggested by the homogeneity of the QTL effect estimates for the F1 sires in the present study. However, previous genome scans for fatness (Bidanel *et al.*, 2001),

IMF (Bidanel *et al.*, 2002) and carcass composition (Milan *et al.*, 2002) pointed out QTL with similar effects with line-cross (Haley *et al.*, 1994) and sib-family models, but they later failed to detect linkage for fatness on SSC7 using line-cross models (Quintanilla *et al.*, 2002), as Knott *et al.* (1998) in a cross between Wild Boar and Large White. Moreover, de Koning *et al.* (1999) reported segregation of QTL alleles for fatness on SSC7 in the Meishan and Dutch breeds. But if true, further line cross analysis should be more powerful (Alfonso & Haley, 1998) and give more accurate estimates so the QTL mapping might be refined. Finally, studies taking account of interactions with the QTL segregating on other chromosomes should be carried out to get a complete picture of the genetic pattern of the traits.

The model with at least 3 chromosomal regions affecting the traits was finally based on 6 individual patterns (Figure 3) which could not be explicitly separated in this study, due to the high number of loci that should be jointly considered. Among those 6 QTL regions, 3 were mapped in the very narrow region surrounding the SLA microsatellite. To distinguish among them using the interval mapping techniques, simulation studies (Knott & Haley, 2000; Korol *et al.*, 2001; Gilbert & Le Roy, 2007) showed that a higher number of informative recombinant individuals should be genotyped for genetic markers located between the different QTL. Alternative methods, such as IBD techniques in linkage disequilibrium approaches, the production of new informative recombinations by *e.g.* backcross designs and the genotyping of additional markers, would be necessary at this stage to narrow the QTL confidence interval.

Three different groups of traits related to different physiological functions were identified. The first group corresponded to internal fat characteristics, *i.e.* intramuscular fat content and leaf fat weight. The second group concerned external fat, with two highly correlated measures of backfat thickness. Different effects between the groups might be related to different kinetics for fat deposition or different compositions between external and internal fat. Finally backfat weight the day after slaughtering seemed isolated in a third group. This differential pattern between the two backfat thickness measurements at slaughter and the backfat weight 24 hours later could be related to the general shape of the backfat, due to different carcass lengths for example, or to fat composition, which may induce different fat weight losses the day after slaughter, suggesting a technological interest of these loci. It is not clear however if the loci influencing backfat weight and thicknesses in the SLA regions were actually different or if the model including BFT1 and BFT2 did explained most of the weight variability. However the second and potential third loci involved in backfat variability seemed to only affect thickness.

Moreover, the differences for “internal” fat and “external” fat on SSC7 were related to a positive effect of the Meishan alleles on intramuscular fat content, associated with a negative influence on the other traits for all the QTL, indicating a cryptic favourable allele for IMF segregating in the Large White breed. Cryptic alleles for fatness have been previously described on SSC7, essentially concerning backfat thickness (Moser *et al.*, 1998; Rohrer & Keele, 1998; de Koning *et al.,* 1999) but they did not seem to be fixed in the grand-parental breeds (de Koning *et al.,* 1999). But the residual correlations beside the QTL effects estimated in our study between IMF and the carcass composition traits were at most close to zero. Other cryptic alleles or more complex mechanisms might thus be driving the genetic correlations between those traits in that particular cross. Combined with narrowed locations, the additional information about the function of the loci will ease searches for functional and positional candidate genes and may help genetic improvement of IMF content, and correlatively meat quality, with no deterioration of carcass composition. Indeed marker assisted selection appears as particularly interesting since accurate phenotyping is expensive and phenotypic and genetic correlations with traits of interest are unfavourable – as IMF compared to genetic parameters of carcass composition and fatness in commercial populations. The identification of a specific locus to be selected for in commercial populations - with no deterioration of the carcass composition – would thus be of major interest.

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