

# Mapping of quantitative trait loci on porcine chromosome 4

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## Summary

A  $F_2$  population derived from a cross between European Large White and Chinese Meishan pigs was established in order to study the genetic basis of breed differences for growth and fat traits. Chromosome 4 was chosen for initial study as previous work had revealed quantitative trait loci (QTLs) on this chromosome affected growth and fat traits in a Wild Boar  $\times$  Large White cross. Individuals in the  $F_2$  population were typed for nine markers spanning a region of approximately 124 cm. We found evidence for QTLs affecting growth between weaning and the end of test (additive effect: 43.4 g/day) and fat depth measured in the mid-back position (additive effect: 1.82 mm). There was no evidence of interactions between the QTLs and sex, grandparents or  $F_1$  sires, suggesting that the detected QTLs were fixed for alternative alleles in the Meishan and Large White breeds. Comparison of locations suggests that these QTLs could be the same as those found in the Wild Boar  $\times$  Large White cross.

**Keywords:** fat, growth, pig, quantitative trait loci

## Introduction

The use of genetic markers is now widespread and marker technology is both accessible and adaptable to many applications. One application of markers is the mapping of quantitative trait loci (QTLs). Most studies in experimental organisms use populations derived from inbred lines. QTL mapping in livestock is more challenging because most populations are outbred and so both markers and QTLs can be segregating within lines. This problem can be reduced by the creation of an experimental population based on a cross between lines or breeds that differ markedly for one or more traits

of interest. In this case it may be reasonable to assume that the two lines are fixed for alternative alleles at major QTLs which simplifies the analysis.

Of the livestock species the pig has several advantages for QTL mapping studies. Diverse, viable breeds exist, three generation pedigrees can be produced relatively quickly and the genetic map of the porcine genome is relatively well developed (Archibald *et al.* 1995; Marklund *et al.* 1996; Rohrer *et al.* 1996). A cross between breeds differing significantly for fat depth and growth rate can detect QTLs affecting these traits. Given the high economic weightings of these traits such findings are of great interest to the pig industry.

The first genome scan in pigs for QTLs used a Wild Boar  $\times$  Large White cross (Andersson *et al.* 1994) and revealed significant effects of QTLs on growth from birth to 70 kg, length of small intestine, average back fat depth and abdominal fat percentage. The QTLs with the largest effects were all on porcine chromosome 4. This population has been examined further with additional markers, confirming these effects (Knott *et al.* 1998). It is both of scientific and commercial interest to know whether similar effects can be found in other breed crosses or within breeds of commercial populations. Identifying economically important regions of the genome segregating within commercial breeding populations would provide criteria for selection to fix beneficial alleles. Introgression of genes from other breeds provides a source of potential breed or line improvement.

The Chinese Meishan breed is genetically distant from European breeds and is known to benefit from a significantly higher litter size (Haley *et al.* 1995) in comparison to European commercial breeds but grows more slowly and is substantially fatter (Haley *et al.* 1992). Composite breeds containing genes from Meishan and European breeds are already being developed for commercial use and so detection of QTLs for traits of commercial value would allow marker-assisted selection in these composites.

We have established an  $F_2$  population to

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determine whether the QTLs detected in the Wild Boar study are segregating in a Meishan × Large White cross. We report here our initial study of QTLs, focusing on chromosome 4.

## Materials and methods

### Animals

The UK population of Meishan pigs were derived from the importation of 11 males and 21 females from the Jiadan county pedigree on the Lou Tang research farm in China in 1987 (Haley *et al.* 1992). The Large White pigs used were from a British control population, derived from a broad sample of genotypes in 1982. All animals in this population were screened to ensure absence of the halothane gene (Cameron *et al.* 1988).

### Genotyping

DNA was prepared by standard procedures from spleen tissue that was collected at slaughter and stored at  $-70^{\circ}\text{C}$ .

Polymorphic microsatellite markers were selected for genotyping on the basis of their map positions on porcine chromosome 4 (Archibald *et al.* 1995; Marklund *et al.* 1996; Rohrer *et al.* 1996) and on the genotypes of the grandparental pigs, which are part of the PiGMap reference pedigrees (Archibald *et al.* 1995). A description of the markers can be found in Table 1. The published PCR conditions were modified as necessary to optimise performance in our laboratory. Each marker was subjected to PCR amplification separately. PCR products were pooled as appropriate and loaded onto an ABI 373 fluorescent DNA fragment analyser (PE Biosystems, Foster City, CA, USA). Data were interpreted and alleles called using ABI Genescan 2<sup>TM</sup> and Genotyper 1<sup>TM</sup> software (PE Biosystems). The genotypes were transferred to the project database, prior to map construction and QTL analysis.

### Experimental design

Two Large White boars were crossed with two Meishan sows. Reciprocally, two Meishan boars were crossed with two Large White sows, all  $F_0$  animals were unrelated. From the  $F_1$  offspring, seven boars were mated to 25 sows from a different grandparental pairing producing  $F_2$  offspring in 43 full-sib families. Each  $F_1$  sow had up to two litters of  $F_2$  pigs. Animals were individually weighed at birth and the number of teats was recorded. Limited cross fostering from the largest litters was used to reduce variation in litter size and animals were weaned between 4 and 5 weeks of age. All animals were weighed individually at weaning. Animals were performance tested in pens of four over a fixed weight range with a target start weight of 30 kg and finished at a target pen weight of 320 kg. All pigs were fed *ad-libitum* on standard commercial growth rations. At the end of test, ultrasonic measurements of back fat depth were taken at the shoulder, mid back and the loin (the criteria for recording these measurements uses the same method as Haley *et al.* 1992). All fat measurements were taken on farm and re-examined from videotape to confirm measurements. Animals without a full test record were discarded from the analysis. Traits analysed and their abbreviations are summarised in Table 2.

### Phenotypic data

The means and SDs for birth weight (BWT) and weaning weight (WWT) in Table 2 are similar to many studies including those involving only European Large White pigs, e.g. Kerr & Cameron (1995). Growth traits were lower and fat traits higher in the  $F_2$  population in comparison to commercial Large White populations but similar to those from studies using Wild Boar (Knott *et al.* 1998) and Meishan (Haley *et al.* 1992) crossbreeds. Similar means to other Meishan crosses (Haley *et al.* 1992) were found for growth rate to

**Table 1.** Markers, their source, dyes and observed fragment lengths used in this study

Marker	Reference	Dye	Observed size range (bp)
S0227	Robic <i>et al.</i> (1994)	HEX	231–257
S0301	Høyheim <i>et al.</i> (1994)	FAM	252–263
S0001	Fredholm <i>et al.</i> (1993)	FAM	178–190
S0023	Coppieters <i>et al.</i> (1993)	TET	80–105
S0217	Robic <i>et al.</i> (1994)	FAM	246–258
S0073	Fredholm <i>et al.</i> (1993)	FAM	107–119
S0214	Robic <i>et al.</i> (1995)	HEX	125–138
SW445	Rohrer <i>et al.</i> (1994)	FAM	192–202
S0097	Ellegren <i>et al.</i> (1993)	TET	220–244

**Table 2.** Summary of traits analysed (means and SDs) from 390 F<sub>2</sub> animals

Trait	Abbreviation	Mean	SD
Birth weight (kg)	BWT	1.25	0.25
Weaning weight (kg)	WWT	8.24	1.86
Growth rate: birth-weaning (g/day)	GRW	254.0	51.3
Growth rate: birth-start of test (g/day)	GRS	375.2	50.6
Growth rate: birth-end of test (g/day)	GRE	481.8	80.0
Growth rate: weaning-start of test (g/day)	GRWS	460.4	80.1
Growth rate: weaning-end of test (g/day)	GRWE	536.9	100.8
Growth rate: on test (g/day)	GROT	581.1	137.6
Fat depth, shoulder (mm)	BFS	33.4	8.30
Fat depth, mid back (mm)	BFM	19.3	6.91
Fat depth, loin (mm)	BFL	20.8	6.78
Mean fat depth (mm)	MF	24.5	6.84
Teat number	TN	15.1	1.13

weaning (GRW), growth rate from weaning to start of test (GRWS) and growth rate on test (GROT). Means for fat depth at shoulder (BFS), mid back (BFM) and loin (BFL) were generally higher in this study than those published in Haley *et al.* (1992). However, measurements of fat traits can vary between data analysts due to the layering of the fat and the higher means could be due to this subjective variation. The data for teat number (TN) are in agreement with Haley *et al.* (1995).

#### Map construction

Marker genotypes that were inconsistent with the pedigree were checked. In the few cases where the genotyping inconsistency could not be resolved, the genotype was set to unknown. F<sub>2</sub> individuals with >2 non-inheritance errors were removed from the analysis. Overall 4.1% of all genotypes were recorded as unknown. This percentage also includes missing data. Once genotypes had been obtained for >90% of the F<sub>2</sub> pigs, the marker was considered complete. Linkage maps were produced using the BUILD option in Cri-Map (Green *et al.* 1990). The CHROMPIC option was used to provide a list of all double recombinants. Parents from families with two or more double recombinants for any marker were re-examined. The completed sex-averaged map used nine markers spanning 124 cm and was compared with previous studies (Archibald *et al.* 1995; Marklund *et al.* 1996; Rohrer *et al.* 1996) to confirm marker order and distance.

#### Information content

Information content was calculated for individual markers and using all available information. Information content quantifies the

amount of information that is available for deriving the QTL genotype at a location on the chromosome. Details on the calculation of information content are given in Knott *et al.* (1998).

#### Statistical analysis

The statistical approach adopted was developed by Haley *et al.* (1994). The analysis carried out works in two stages; firstly, the probability of the F<sub>2</sub> offspring being each of the four possible QTL genotypes is calculated conditional upon the marker genotypes. Secondly, these probabilities are then used in a least squares framework to investigate the genetic model underlying the trait of interest.

The expected value of the offspring can be written as a linear model in terms of additive and dominance contributions for the QTL:  $y_i = \mu + c_{ai}a + c_{di}d + e_i$ ; where  $\mu$  is the mean,  $a$  the additive effect of the QTL,  $d$  the dominance effect of the QTL,  $c_{ai}$ ,  $c_{di}$  and  $e_i$  are the expected additive, dominance and residual error levels of expression of the QTL on an individual  $i$  at a given location, respectively. This equation can be easily expanded to incorporate both fixed effects and covariates into the model.

The model used for analysis of all traits included fixed effects of family and sex. The model for WWT included BWT as a covariate. Models for fatness traits included covariates of age and weight at end of test. Models for growth traits included the weight at start of period (e.g. the model for GROT included weight at start of test) as a covariate.

#### Thresholds

Chromosomal and suggestive (Lander & Kruglyak 1995) significance thresholds were set by

the Churchill & Doerge (1994) permutation test of the chromosome 4 data. The Bonferoni correction was used to calculate a genome wide threshold from the chromosomal Churchill & Doerge (1994) permutation test. The 5% genome threshold was calculated as the  $(5/19) = 0.263\%$  chromosomal threshold to account for the 17 other autosomes and X-chromosome (5% threshold over 19 chromosomes). This assumes 19 independent chromosomes each having an equal probability of producing a type 1 error.

#### *Alternative genetic models*

Initially, the chromosome was searched every centimorgan by regressing the phenotypes onto the coefficients of *a* and *d*. At each location an *F*-ratio was calculated comparing the model that included a QTL to the equivalent model with no QTL. Estimates for *a* and *d* were calculated at the best estimated position on the chromosome as determined by the position with the highest *F*-ratio. The test statistic was therefore an *F*-ratio with 2 d.f. in the numerator.

If the *F*-ratio in the initial analysis exceeded the threshold, we tested for a QTL  $\times$  sex interaction to investigate whether the effect differed between the two sexes. In order to look for evidence that a QTL was segregating in one or other of the purebred lines, we also included a series of analyses looking for interactions between the QTL effect and family. First, interactions were tested with combinations of grandparents to test whether the QTL effect varied dependant upon grandparental origin. There were four pairs of grandparents (each pair being one Meishan and one Large White animal) and hence there were six possible combinations of grandparents (as  $F_1$  animals were not mated to full-sibs). Thus, in the interaction analysis a separate QTL effect was estimated for each of these six possible combinations. Second, an interaction was also fitted with the seven  $F_1$  sires in order to determine whether the QTL effect differed in  $F_2$  families according to their sire. The interaction models were tested against the equivalent model with no QTL and the model with a QTL but no interaction.

A trait showing evidence for a single QTL was also tested for the presence of two QTLs. The two QTL model fits two QTLs by fixing one of the QTLs and searching at 5 cm intervals along the chromosome before moving the fixed QTL to the next location (also spaced at 5 cm). This model was also tested by *F*-ratio against a model with no QTL and against a model with only one QTL.

## Results

### *Linkage map*

The linkage map developed from the  $F_2$  population is presented in Fig. 1. The map is in close agreement with other studies (Archibald *et al.* 1995; Marklund *et al.* 1996; Rohrer *et al.* 1996). There was a significant difference between the maps of the two sexes ( $\chi_8^2 = 105.5$ ), with the female linkage map being significantly longer. The QTL analyses used the sex-averaged map. The information content along the chromosome and of individual markers is presented in Fig. 2. Markers were evenly spaced throughout the chromosome maintaining the information content above 0.6. Markers S0214 and S0023 were relatively low in information content because they had a relatively high frequency of shared alleles between breeds.

### *Thresholds*

The 5% genome-wide significant and suggestive thresholds were similar for all traits. All traits gave genome significance thresholds between 8.5 and 9.1 and suggestive thresholds between 5.0 and 5.2. These results are in agreement with Knott *et al.* (1998), who performed their permutation analysis using data from an entire genome scan.

### *One QTL model*

The results for the one QTL search for all traits are summarised in Table 3. The analyses of data showed significant evidence for QTLs affecting several traits; these were GRS, GRE, GRWS, GRWE, GROT and BFM. The analyses of data for BFS and MF showed suggestive evidence for a QTL. Given that many of the growth periods overlap, some of these traits were correlated. However, the analyses of the two non-overlapping periods (GRWS and GROT) both indicated QTLs, although in slightly different positions (42 and 69 cm) on chromosome 4. This result could be the same QTL acting from weaning to the end of test or two different QTLs acting at different stages of growth. Graphs of the *F*-ratio along chromosome 4 for GRWS, GRWE, GROT and BFM are presented in Fig. 3.

### *Two QTL model*

Results for the two QTL analyses are presented in Table 4. Two of the traits fit a two QTL model significantly better than the one QTL model at the nominal 5% significance level. The analyses for BFM place two QTLs very close together

with the same effects of similar size, but of opposite signs. The work of Whittaker *et al.* (1996) demonstrated that it was impossible to locate two QTLs within an interval, because four parameters (additive and dominance effects for two QTLs) are estimated from two regression coefficients on markers. There is a set of solutions that satisfy the relevant equations (Whittaker *et al.* 1996) but this result produces unfeasibly large and opposite estimates of the genetic effects and is clearly untenable. The two QTL analyses for GRWS fits two QTLs at 40 and 115 cm. A two QTL search at 1 cm intervals along the chromosome for GRWE (results not presented) fit the two QTL model significantly better than the one QTL model at the 5% significance level placing QTLs at 42 and 69 cm. These results correspond to the double peak in Fig. 3 for GRWE and would also explain the positional difference between the one QTL model for GRWS and GROT.

Results for the interaction analyses are presented in Table 5. Several traits showed significant interactions when the best model with an interaction was compared with best model without an interaction regardless of the relative

positions of the QTLs in the two models. When the models were compared at a fixed position of the best model with no interaction no traits showed significant evidence for an interaction (results not shown).

## Discussion

In this study we detected QTLs with major effects on growth rate and subcutaneous fat depths on chromosome 4. It is of great interest to know if these QTLs are the same as those detected by Andersson *et al.* (1994). In Fig. 4 we compare the approximate confidence intervals for both growth rate and fat depth QTLs from this study with those from the Wild Boar cross population. Alignment of the maps is approximate because as only three markers (indicated on the map) were common to both studies. Comparisons between studies have to be treated carefully with caution as traits are measured differently in each study. The QTL in the Wild Boar population for back fat was reported to have an additive effect of 2.3 (Andersson *et al.* 1994) and 2.0 mm (Knott *et al.* 1998) when fat measurements of fat depth were taken at

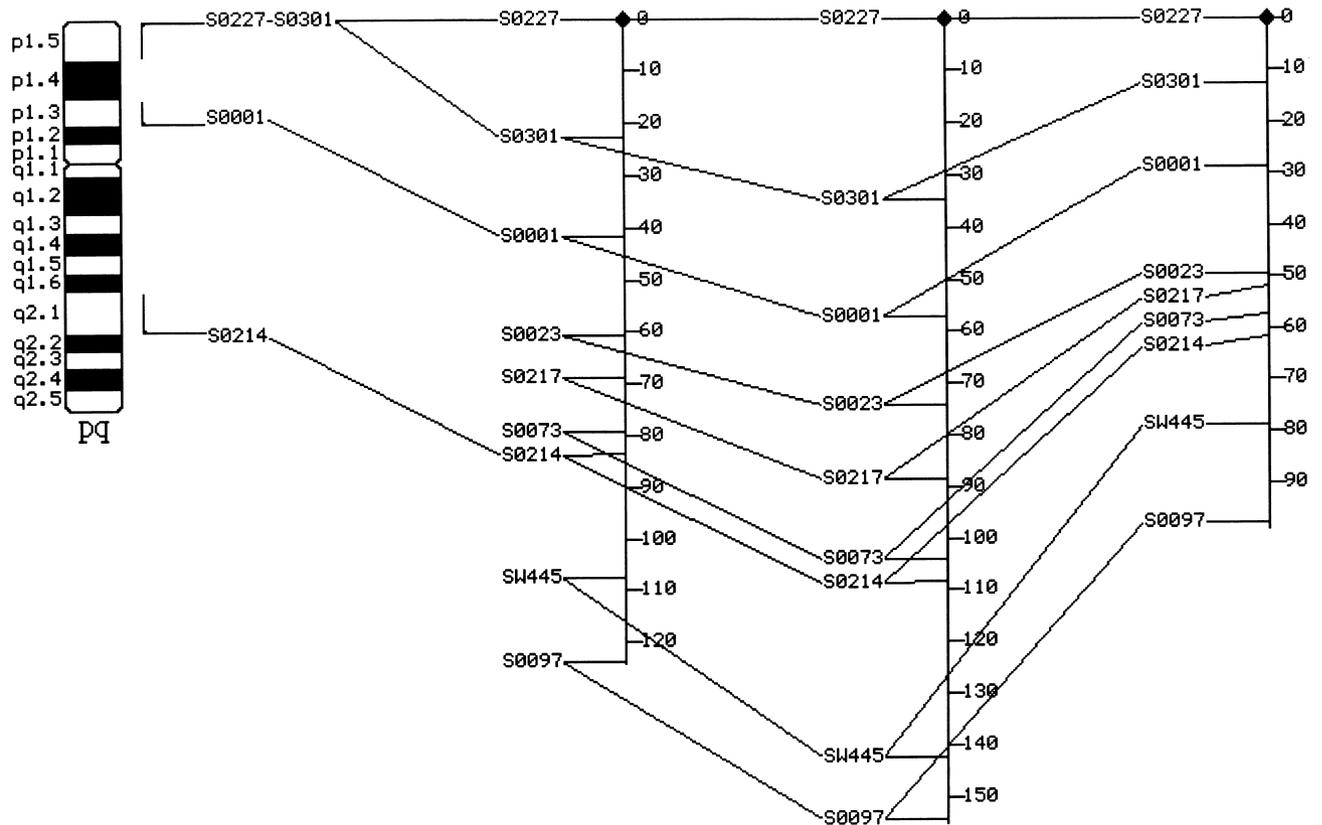


Fig. 1. Chromosome 4 maps: (from left to right) cytogenetic map (Marklund *et al.* 1993; Høyheim *et al.* 1994; Robic *et al.* 1995), sex averaged, female and male linkage map for markers used on chromosome 4. The map display was developed using the Anubis map viewer (Mungall 1996; [http://www.ri.bbsrc.ac.uk/genome\\_mapping](http://www.ri.bbsrc.ac.uk/genome_mapping)).

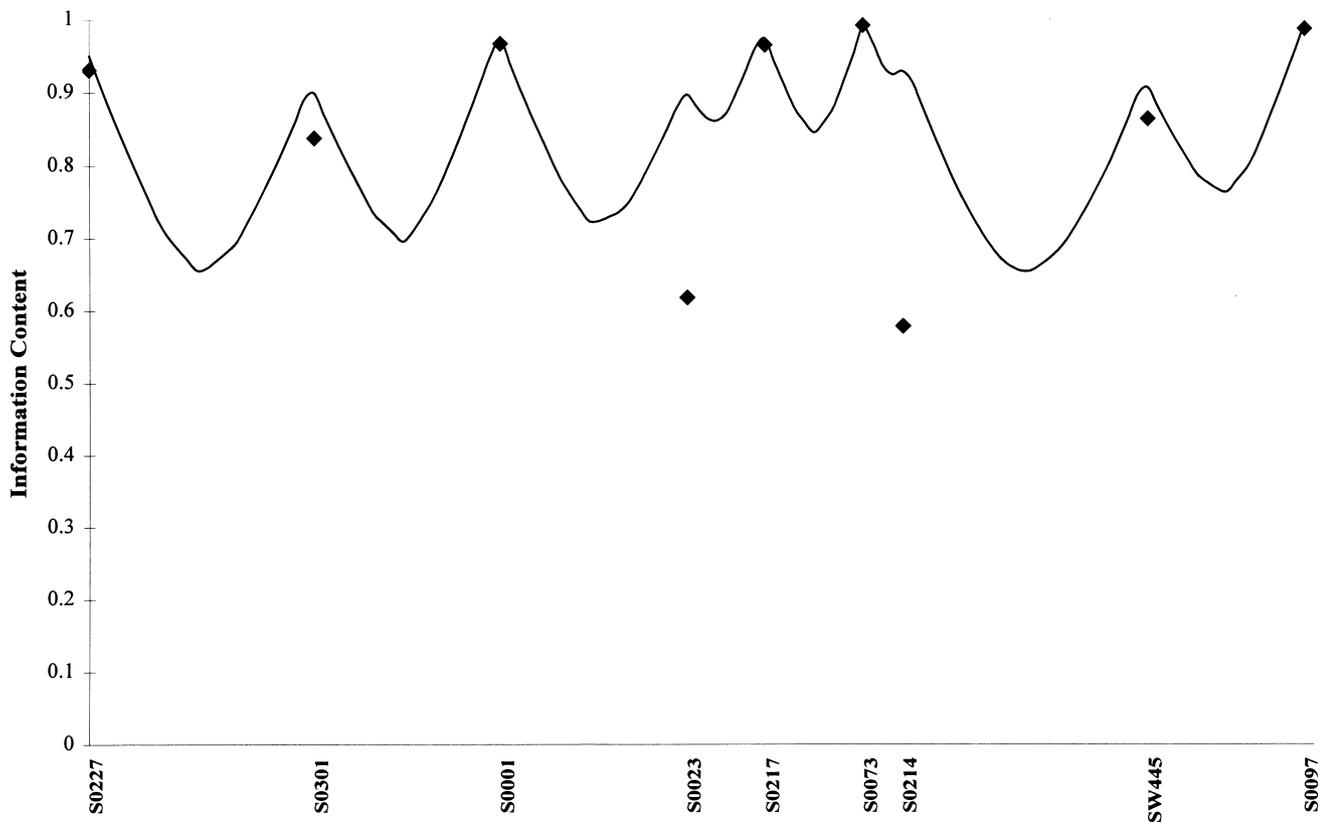


Fig. 2. Information content along chromosome 4 of single markers (individual points) and using all information (solid line). Positions of markers are indicated along the x-axis.

slaughter. In the Wild Boar study the fat depths represented an average of five measurements along the dorsal mid line at shoulder, last rib and loin. Both studies analyses of the Wild Boar population placed the QTL approximately 30 cm from S0001 (Andersson *et al.* 1994; Knott *et al.* 1998). The QTL for back fat detected in our Meishan F2 population had an additive effect of 1.8 mm and was placed within the same region. The similarity of results between the studies can be seen in Fig. 4 where all confidence intervals for fat share a common region between S0175 and GBA.

The growth traits studied are slightly different between the two populations. Andersson *et al.* (1994) found a QTL having an additive effect of  $23.5 \pm 4.9$  g/day for growth rate from birth to 70 kg. Knott *et al.* (1998) with more marker data from the same population found a QTL having an effect of  $14.6 \pm 4.0$  g/day for the same trait. Both studies placed the QTL approximately midway between markers S0001 and S0097 that corresponds to the estimated position for the QTL affecting GROT in this study. The similarity of results between the studies can be seen in Fig. 4 where all growth rate confidence intervals encompass the region of chromosome 4

between S0001 and S0073. In our Meishan  $\times$  Large White population the additive effect is significantly larger ( $51.9 \pm 9.5$  g/day). The reason for this difference in size could possibly be due to the differences in the experiments or the different genetic backgrounds of the Meishan and Wild Boar. GROT only incorporates the period of growth between  $\approx 30$  and 80 kg, while the Wild Boar study measured growth rate from birth until a similar end weight (70 kg). By incorporating the birth to 30-kg period, the mean detected additive effect is reduced because of the slower growth rate during early development. The closest equivalent trait in our Meishan study is GRE, the additive effect of the QTL for this trait is  $33.7 \pm 5.6$  g/day, this result is closer to that seen in the Wild Boar study.

It is interesting to note that neither this study nor those of the Wild Boar cross give clear single peaks on the test statistic curve for the QTLs affecting growth rate. The data from this study provides limited evidence (significant at the nominal significance level) for two QTLs affecting growth rate. The separate analyses of GRWS and GRWE suggest that these QTLs could have different effects on these two stages of growth, one acting between weaning and start of test

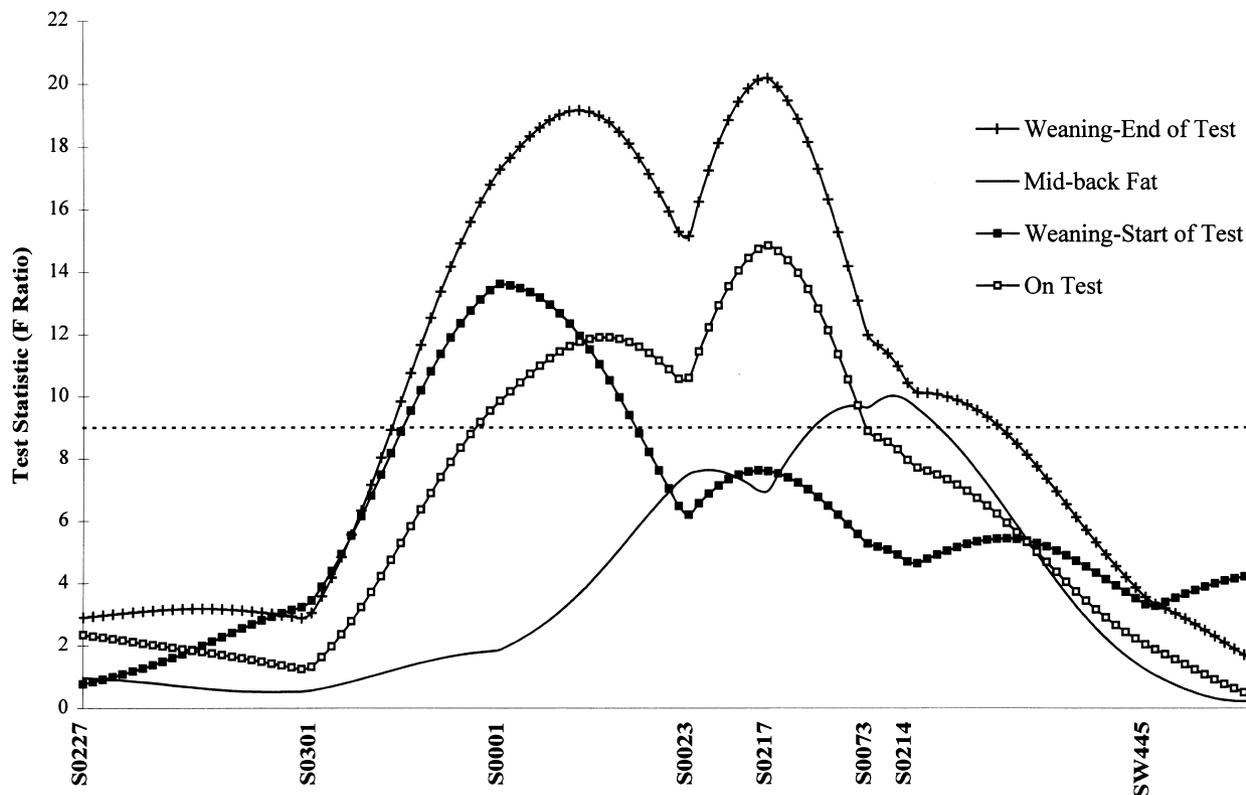
**Table 3.** Best estimated positions and effects from fitting one QTL

Trait	Covariates	F-Ratio	Location (cm)	Additive (SE)	Dominance (SE)
BWT		1.72	124	5.7 (17)	59.0 (25.6)
WWT	BWT	2.47	76	-3.2 (8.8)	285.6 (129.7)
GRW		2.43	108	-1.33 (3.05)	9.84 (4.49)
GRS		10.1	43	12.2 (3.2)	12.3 (4.7)
GRE		18.2	68	33.7 (5.6)	8.8 (8.0)
GRWS	WWT	13.6	42	23.6 (4.8)	13.8 (6.9)
GRWE	WWT	20.2	69	43.4 (6.8)	7.7 (9.7)
GROT	Start weight	14.8	69	51.9 (9.5)	10.3 (13.5)
BFS	Age at end End weight	6.6	81	-1.79 (0.51)	0.36 (0.70)
BFM	Age at end End weight	10.0	82	-1.82 (0.41)	0.16 (0.57)
BFL	Age at end End weight	4.2	79	-1.17 (0.40)	-0.10 (0.54)
MF	Age at end End weight	8.5	81	-1.59 (0.39)	0.16 (0.54)
TN		4.21	57	-0.29 (0.09)	0.00 (0.14)

Fixed effects of sex and family were fitted for all traits. Additive and dominance effects for the Large White alleles. BWT and WWT both in kg, all growth rate traits given in g/day and fatness traits in mm.

with an additive effect of 23.6 g/day and the other acting between start and end of test with an effect of 51.9 g/day. However, the 5% nominal significance threshold is probably too relaxed because multiple tests were performed for all combinations of 5 cm pairings of two

QTLs. Of the traits examined (see Table 4), none fit a two QTL model better than the one QTL model below a 2% nominal significance level. The rigid genome threshold attached to the one QTL search of an  $F$ -ratio of 9 is equivalent to a nominal significance level of 0.26%. The failure



**Fig. 3.** Test statistic ( $F$ -ratio) of four significant traits across porcine chromosome 4. The genome-wide significance threshold of 9 is marked (horizontal dotted line).

**Table 4.** Results from fitting a two QTL model at 5 cm intervals on traits showing significant results for one QTL

Trait	F-Ratio		P-Value vs. 1 QTL	Location (cm)	Estimates	
	vs. 0 QTL	vs. 1 QTL			Additive	Dominance
GRS	5.97	1.81	0.17	40	12.1 (3.8)	10.6 (5.0)
				80	1.2 (3.9)	9.4 (4.8)
GRE	10.35	2.48	0.09	45	17.8 (7.7)	4.2 (9.6)
				70	21.4 (7.7)	7.9 (9.3)
GRWS	8.48	3.24	0.03	40	21.4 (5.1)	14.9 (6.5)
				115	14.7 (6.5)	19.2 (11.7)
GRWE	11.43	2.72	0.07	45	23.2 (9.5)	3.8 (11.9)
				70	27.8 (9.5)	6.7 (11.4)
GROT	7.76	0.88	0.42	45	18.6 (13.3)	-6.0 (16.7)
				70	39.7 (13.2)	14.0 (15.9)
BFM	6.87	3.93	0.02	85	-10.7 (3.6)	5.6 (4.1)
				90	10.0 (3.9)	-6.9 (5.0)

Units for the additive and dominance effects are as Table 3.

of the two QTL model to fit the data better than the one QTL model below a 2% significance suggests these data alone do not carry sufficient evidence for two QTLs and further data are needed to explore this possibility.

These results support the hypothesis that the QTLs for fat depth and growth rate identified in this study are the same as those identified in the Wild Boar  $\times$  Large White cross. Furthermore, the alleles segregating appear to have similar effects in the two crosses.

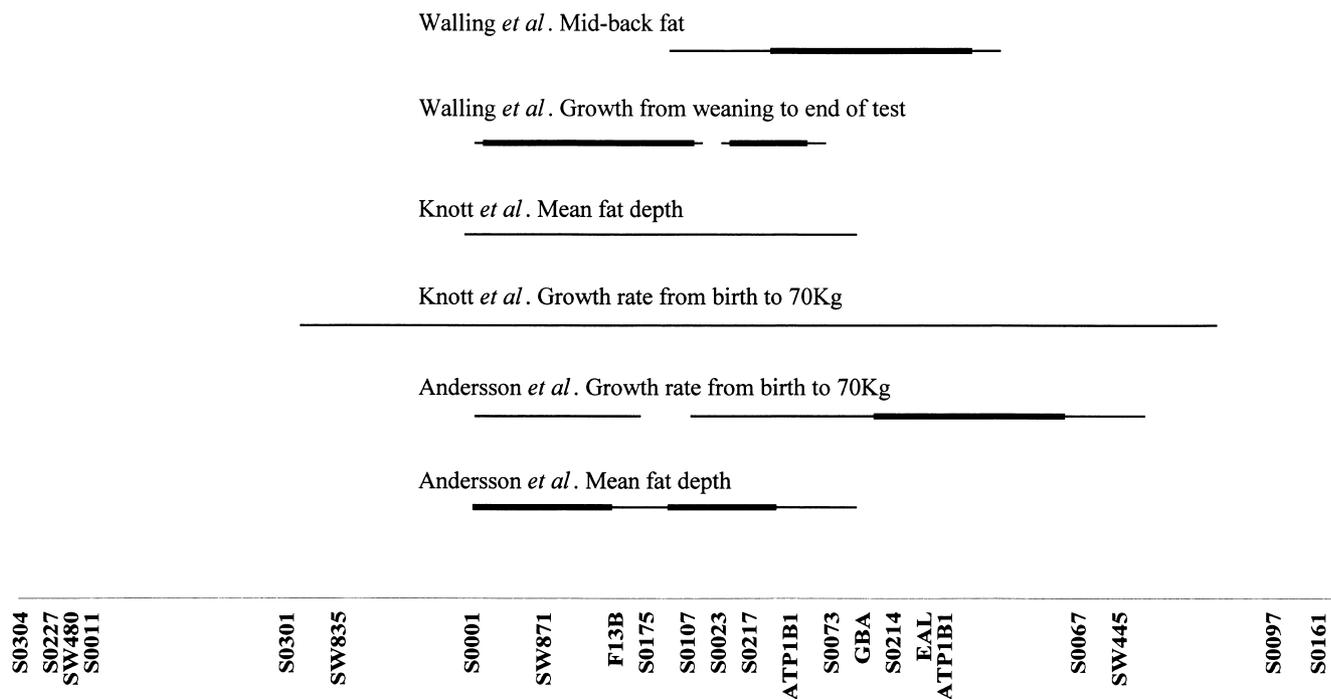
The absence of any significant interactions between the QTL and the grandparental combinations or  $F_1$  sires suggests that the detected QTLs are fixed for alternative alleles in the Meishan and Large White founders. Although the number of founders is very limited, the

Meishan and the Wild Boar may be fixed for the same alleles and the Large White is fixed for an alternative (and presumably more recently derived) allele. It will be very interesting to see if there is evidence for genetic variation in this region affecting growth rate and fatness in Western commercial breeds of pigs.

The results reported here potentially allow for direct exploitation of these chromosome 4 QTLs in composite lines of pigs containing genes from Meishan and Western breeds. In addition, these results provide further impetus for studies of this region in other crosses and within breeds, which could lead to further opportunities for marker-assisted selection. Finally, the identification of these effects in a second cross provides a valuable resource to

**Table 5.** Results from fitting interactions with sex, combinations of grandparents and  $F_1$  sires compared to the model with one QTL with no interaction on traits with significant results for one QTL

Trait	Interaction	F-Ratio vs. 1 QTL with no interaction	P-Value
GRS	Sex	1.81	0.17
	GP combinations	0.61	0.32
	$F_1$ sire	0.81	0.64
GRE	Sex	0.02	0.98
	GP combinations	1.45	0.16
	$F_1$ sire	1.98	0.03
GRWS	Sex	0.64	0.53
	GP combinations	1.21	0.28
	$F_1$ sire	1.63	0.08
GRWE	Sex	0.30	0.74
	GP combinations	1.70	0.08
	$F_1$ sire	2.41	0.01
GROT	Sex	0.37	0.69
	GP combinations	1.98	0.03
	$F_1$ sire	2.40	0.01
BFM	Sex	0.63	0.53
	GP combinations	1.16	0.32
	$F_1$ sire	1.12	0.34



**Fig. 4.** Comparison of confidence intervals for growth and fat QTLs on porcine chromosome 4. Thick line is a one LOD drop (Lander & Botstein 1989), thin line a two LOD drop. Knott *et al.* (1998) produced 95% confidence interval using a bootstrap method (Visscher *et al.* 1996).

aid attempts to identify the genes responsible for these effects.

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