Combined Analyses of Data From Quantitative Trait Loci Mapping Studies: Chromosome 4 Effects on Porcine Growth and Fatness

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ABSTRACT

For many species several similar QTL mapping populations have been produced and analyzed independently. Joint analysis of such data could be used to increase power to detect QTL and evaluate population differences. In this study, data were collated on almost 3000 pigs from seven different F_2 crosses between Western commercial breeds and either the European wild boar or the Chinese Meishan breed. Genotypes were available for 31 markers on chromosome 4 (on average 8.3 markers per population). Data from three traits common to all populations (birth weight, mean backfat depth at slaughter or end of test, and growth rate from birth to slaughter or end of test) were analyzed for individual populations and jointly. A QTL influencing birth weight was detected in one individual population and in the combined data, with no significant interaction of the QTL effect with population. A QTL affecting backfat that had a significantly greater effect in wild boar than in Meishan crosses was detected. Some evidence for a QTL affecting growth rate was detected in all populations, with no significant differences between populations. This study is the largest F_2 QTL analysis achieved in a livestock species and demonstrates the potential of joint analysis.

THE use of genetic markers to detect regions of the genome associated with quantitative traits is now widespread. Some agricultural species have been the focus of particular attention because of the potential benefits of detecting and identifying quantitative trait loci (QTL) and using them in marker-assisted breeding programs.

These data have only been analyzed separately so far, but, in theory, joint analysis offers considerable potential to extract additional information from the data. For example, joint analysis of two or more similar populations could lead to more power to detect QTL not found in any individual study or could be used to confirm the presence of QTL detected in only one population (Lander and Kruglyak 1995). Joint analysis could potentially lead to more precise estimates of the effects and location of a common QTL and could be used to examine differences in QTL effects in different populations. In practice, however, there are a number of problems to be resolved before joint analyses can be performed. For example, different markers may be used in different populations, the individuals are reared in different environments and with different testing regimes, and recording of traits differs between studies.

Several different groups have produced QTL mapping resource populations on the basis of crosses between genetically diverse pig populations. Reports of QTL studies of the porcine genome have been based previously on an individual population and hence a limited number of animals. Joint analysis has never been attempted within the porcine genome mapping projects but offers greatly increased power because together there are data on markers and performance traits on >3000 F_2 animals. This study was established to investigate possible benefits and drawbacks of the joint analysis of several different data sets involved in the European Commission pig genome mapping project. A single chromosome, chromosome 4, was chosen, as data from the individual trials suggested that large QTL effects would be found in several populations (Andersson *et al.* 1994; Knott *et al.* 1998; Milan *et al.* 1998; Moser *et al.* 1998; Walling *et al.* 1998; Wang *et al.* 1998; de Koning *et al.* 1999).

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TABLE 1

Source of material, population code, breed cross, and F_2 population size (for birth weight) for data used in the joint analysis

Source	Code	Cross	F_2 population size
Roslin Institute (Edinburgh), Roslin, Midlothian, UK	GB	Large White × Meishan	390
Institut National de la Recherche Agronomique, France	FR	Large White × Meishan	896
Wageningen Agricultural University, Wageningen, Netherlands	NL	Large White or Landrace × Meishan	586
Iowa State University, Ames, IA	US	Duroc or Hamshire or Landrace × Meishan	249
University of Hohenheim, Stuttgart, Germany	D (ms)	Piétrain × Meishan	314
	D (wb)	Piétrain × wild boar	298
Swedish University of Agricultural Sciences, Uppsala, Sweden	SW	Large White × wild boar	199

MATERIALS AND METHODS

Data: Data were collected from collaborators in six different countries. All populations were based on F_2 crosses between genetically divergent breeds. The source of the populations, their sizes, and the various crosses of which they consist are summarized in Table 1. A single population was defined for data from each country, with the exception of the German data, which was split into Meishan- and wild-boar-derived populations for the analyses. The total number of F_2 animals recorded for birth weight and genotyped was 2932; this was reduced to 2842 for fat depth, which was recorded at the end of test.

Data editing: Individuals with no marker genotype information available were omitted from the analyses. Similarly, animals missing trait data or data required to be used as covariates were also omitted from the analyses. Three traits were chosen for analysis that had similar definitions in all populations. These traits were birth weight (BWT), growth rate (weight gain over time, g/day) from birth to end of test or slaughter (GRE), and subcutaneous fat depth at end of test (FAT). The end of the growth rate test period and the measurement of subcutaneous fat depth differed between populations as summarized in Table 2.

Map construction: No individual marker was common to all seven populations. On average, each marker was typed in two populations with any two populations having 2.7 markers in common. The linkage map was produced using Cri-Map (Green *et al.* 1990). The marker order was explored using the FLIPS command until the marker order maximizing the likelihood was obtained. The complete sex-averaged map (Figure 1) used 31 markers spanning 145 cM and was within the range of lengths from previous studies (Archibald *et al.* 1995; Marklund *et al.* 1996; Rohrer *et al.* 1996). Average marker spacing on the composite map was 4.7 cM. Although information content was typically low for individual markers, often because they were only scored in some of the populations, overall information content was high. Information content across the entire chromosome using all available markers remained >0.59.

Statistical analysis: The statistical approach adopted for QTL analysis was that developed by Haley *et al.* (1994) for a cross between outbred lines. The analysis is applied in two stages: First, the probability of an F_2 offspring being each of the four QTL genotypes (QQ, Qq, qQ, and qq) at each position in the genome is calculated conditionally upon the marker genotypes. Second, a linear model for the additive (*a*) and dominance (*d*) effects of a QTL at a given position is applied by least squares for each trait of interest. The analysis assumes that QTL are fixed for alternative alleles in the two breeds. All QTL analyses, including those of individual populations, were based on intermarker distances from the joint map, derived as described above.

Least squares model fitted: The model for all traits included sex and F_2 family nested within population as fixed effects. Feed treatment on test was fitted as a fixed effect from the

TABLE 2

Differences in test procedure and fat measurement between different populations

Population	End of test	FAT
FR	Females 150 days; males 160 days	Mean of two measures at each of shoulder, last rib, and hip (Milan *et al.* 1998)
GB	80 kg	Mean of shoulder, midback, and loin (Walling *et al.* 1998)
D (ms)	210 days	Mean of neck, loin, and hip (Geldermann *et al.* 1996)
US	110 kg	Mean of first rib, last rib, lumbar, and 10th rib (Rothschild *et al.* 1995)
NL	85 kg	Single measure between 3rd and 4th ribs (Janss *et al.* 1997)
SW	70 kg	Mean of five measurements along dorsal midline (Andersson *et al.* 1994)
D (wb)	210 days	Mean of neck, loin, and hip (Geldermann *et al.* 1996)

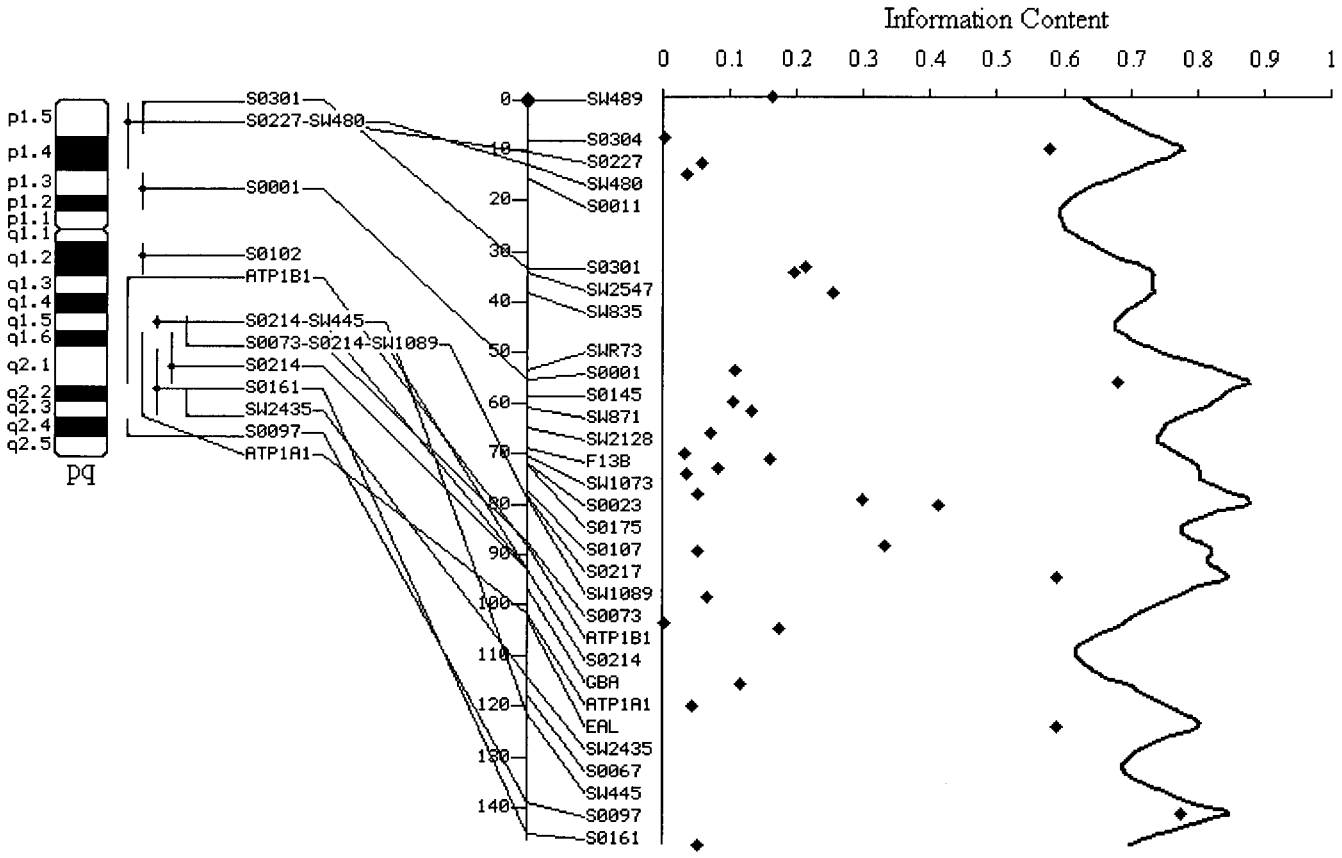

Figure 1.—Chromosome 4 map and information content for the joint analyses. The map display was developed using the Anubis map viewer (Mungall 1996). The solid line represents information content when all markers are used and single points indicate the information content of individual markers.

Swedish data for both growth rate to the end of test or slaughter (GRE) and average backfat depth (FAT). For the joint analyses, feed treatment was fitted within the Swedish population. The model for GRE included birth weight (BWT) as a covariate and the model for FAT included weight at end of test or slaughter as a covariate.

Single-population analyses: The populations were initially analyzed separately. Although single-population analyses have been previously attempted independently with all of the populations (Knott *et al.* 1998; Milan *et al.* 1998; Moser *et al.* 1998; Walling *et al.* 1998; Wang *et al.* 1998; de Koning *et al.* 1999), we conducted separate analyses to allow comparison of the data under the same methodology and statistical model. The chromosome was analyzed by fitting the model at 1-cM intervals, regressing offspring phenotypes onto the coefficients of additive and dominance for a single QTL. For each location, the *F*-ratio of the model with a QTL *vs.* the same model without a QTL was calculated. This *F*-ratio has 2 d.f. for the numerator. The estimated position for a single QTL was taken to be the location with the largest *F*-ratio (Haley *et al.* 1994).

Joint analyses, one QTL: Phenotypic data were standardized to residual standard deviation units for each population. The chromosome was searched as with the single-population analyses. The analyses grouped wild boar and Meishan as one fixed "breed" and the commercial breeds as another. The assumption of this analysis is that there is a single QTL with the same effect in all populations, *i.e.*, the Meishan and wild boar are fixed for one allele and the commercial breeds are all fixed for an alternative allele. The *F*-ratio for this analysis has 2 d.f. for the numerator.

Joint analyses, one QTL with population interaction: To investigate whether the effect of the QTL was different in distinct populations, additive and dominance effects were estimated separately for each population. This model was compared with the model with no interaction for a single QTL at the position estimated for the QTL under this latter model. This test produces an *F*-ratio with $2(n - 1)$ d.f. in the numerator, where n is the number of populations analyzed.

Joint analyses, one QTL with breed interaction: To investigate whether the effect of the QTL was different in Meishan *vs.* wild boar crosses, additive and dominance effects for a single QTL were estimated for each breed. This model was compared with the model with no interaction for a single QTL at the position estimated for the QTL under this latter model. This test produces an *F*-ratio with 2 d.f. in the numerator and is equivalent to a three-allele model assuming one allele common to western breeds and two different alleles in wild boar and Meishan populations.

Breed analyses, one QTL: QTL were analyzed in populations consisting of only Meishan or only wild boar crosses. Here a model assuming different QTL effects between populations within breed cross was compared with one assuming the same effect in different populations within breed cross at the position estimated under the latter model.

Thresholds: This study focuses on a single chromosome where QTL have been detected in more than one population; thus it might be argued that a genome-wide significance thresh-

old is too stringent. However, we expect that future joint analyses may be used to scan the entire genome and a major aim of this study is a comparison with genome scans based on individual studies. Thus, for the sake of comparison we use a genome-wide significance threshold. We do not propose to adjust the threshold for the fact that three traits are analyzed, because such an adjustment would obscure comparisons between different studies in which differing numbers of traits have been recorded.

Due to the large size of the data set (almost 3000 individuals for BWT), thresholds calculated using the Churchill and Doerge (1994) permutation analysis require large amounts of CPU time. Following Knott *et al.* (1998) and Walling *et al.* (1998), the thresholds for the genome-wide and suggestive levels (Lander and Kruglyak 1995) show little variation between traits. Approximate significance levels were therefore based on those from Knott *et al.* (1998). The 5 and 1% genome-wide significance levels used were *F*-ratios of 9.0 and 11.0, respectively. The suggestive significance level used was an *F*-ratio of 5.0.

Two QTL: Due to the large amount of CPU time required a two-dimensional QTL search was carried out only for GRE. GRE produced strong evidence for a QTL in the joint analyses with no significant interactions with population, but nonetheless there was large variation in the estimated QTL position between the single-population analyses. A grid search approach was used (*e.g.*, Haley and Knott 1992), with two QTL fitted at all possible combinations of 5-cM intervals on the chromosome. The best-fitting model with two QTL was tested against the best model fitting with only one QTL (an *F*-ratio with 2 d.f.).

Confidence intervals: A confidence interval for GRE was constructed using the bootstrap approach (Visscher *et al.* 1996). Due to the computing time required, only 100 bootstrap resamples were used. Removing the top and bottom 2.5% of resampled estimates created the estimated 95% confidence interval. This confidence interval was compared to confidence intervals produced from the bootstrap approach for each individual population for GRE. For the bootstrap estimation of confidence intervals of individual populations, 200 bootstrap resamples were used.

This was not repeated for BWT and FAT because there was differing evidence between populations for QTL affecting these traits. In these circumstances, the validity of confidence intervals, constructed from populations with little evidence for QTL, may be limited. GRE was chosen because the majority of the populations contained some evidence for a QTL affecting growth.

RESULTS

Single-population analyses: The results from the single-population analyses are presented in Table 3. For each trait, in each population, the table provides the estimated position of a QTL. The *F*-ratio and the additive effect of the Large White allele are given for the estimated position. Although the methodology differed, the evidence for a QTL did not vary between the previous publications (Knott *et al.* 1998; Milan *et al.* 1998; Moser *et al.* 1998; Walling *et al.* 1998; Wang *et al.* 1998; de Koning *et al.* 1999) and the analyses attempted within this study. Only the French data showed significant evidence for a QTL effecting BWT, although the Dutch data produced an *F*-ratio that approached the suggestive significance threshold. Both the French and the Swedish data showed significant evidence at a genome level for a QTL affecting FAT. This was in a similar estimated position (74 and 83 cM, respectively) but the estimated additive effect differed between the two populations (-1.12 ± 0.18 and -2.39 ± 0.43 mm). The British fat data produced suggestive evidence for a QTL, with a similar estimated position (90 cM) to the French and Swedish studies and an estimated additive effect close to that in the French data (-1.37 ± 0.39 mm). Although not significant, the German wild boar data produced evidence for a QTL with an estimated position and additive effect similar to these other studies (75 cM and -1.11 ± 0.40 mm, respectively).

Analysis of GRE produced substantial evidence for QTL, with some consistency across different populations. The estimated position of a QTL varied between 60 cM in the Swedish population to 99 cM in the German wild boar population. This region encompasses the region of estimated QTL positions for FAT. The estimated additive effects varied from 12.1 ± 4.9 g/day in the

TABLE 3

Results from the individual population analyses

Trait	BWT (g)	GRE (g/day)	FAT (mm)
FR			
F-ratio	13.1***	10.5**	18.8***
Position	75	89	74
Effect (SE)	50 (10)	14.6 (3.6)	−1.12 (0.18)
GB			
F-ratio	1.7	21.3***	6.4*
Position	145	78	90
Effect (SE)	−10 (17)	34.4 (5.3)	−1.37 (0.39)
D (ms)			
F-ratio	2.6	9.0**	4.1
Position	3	75	43
Effect (SE)	38 (25)	19.1 (5.0)	+1.28 (0.47)
US			
F-ratio	2.7	2.8	0.9
Position	19	83	93
Effect	−14 (47)	15.4 (8.0)	−0.26 (0.68)
NL			
F-ratio	4.7	3.4	2.0
Position	92	88	87
Effect (SE)	22 (12)	12.1 (4.9)	0.32 (0.25)
SW			
F-ratio	2.5	7.5*	15.9***
Position	47	60	83
Effect	47 (22)	16.6 (4.4)	−2.39 (0.43)
D (wb)			
F-ratio	1.6	4.7	4.0
Position	122	99	75
Effect	−47 (31)	21.0 (6.9)	−1.11 (0.40)

For each trait in each population, the estimated QTL position is given with the *F*-ratio and additive effect of the allele from the commercial breed at that position together with the estimated standard error (SE). * Suggestive significance; ** 5% genome-wide significance; ***1% genome-wide significance.

TABLE 4

Results from the joint analyses of the chromosome 4 data

Trait	BWT (g)	GRE (g/day)	FAT (mm)
Joint			
F-ratio	9.6**	39.4***	24.8***
Position	85	81	86
F (Int *vs.* no QTL)	2.6	6.9	5.9
F (Int *vs.* no Int)	1.4	1.5	2.6
P (Int *vs.* no Int)	0.164	0.12	0.002
Effect (SE)			
FR	26 (6)	20.3 (2.3)	−1.23 (0.20)
GB	28 (6)	20.6 (2.3)	−1.41 (0.46)
D (ms)	35 (8)	16.6 (1.9)	0.15 (0.35)
US	30 (7)	17.6 (2.0)	−0.01 (0.86)
NL	21 (5)	17.7 (2.0)	−0.19 (0.25)
SW	23 (5)	11.9 (1.3)	−2.57 (0.49)
D (wb)	29 (7)	12.7 (1.4)	−1.20 (0.5)

For each trait, the estimated QTL position is given with the *F*-ratio at that position. The estimated QTL effects are calculated by the residual standard deviation multiplied by the additive effect of the commercial breed allele. The same additive effect for all populations is used if the interaction model is not significantly better than the model with no population interaction. The interaction model is significantly better for FAT; therefore, the additive effects used to calculate the effect of the commercial breed allele were different for each population. *Suggestive significance; **5% genome-wide significance; ***1% genome-wide significance.

Dutch population to 34.4 ± 5.3 g/day in the British population. Evidence for a QTL was at the genome significance level in the French, British, and German Meishan populations and at the suggestive level in the Swedish population. In the US, Dutch, and German wild boar populations the evidence was not significant at the suggestive level, although the latter population approached suggestive significance.

Analysis of the three traits failed to produce any consistent evidence for dominance effects; indeed the number of significant results did not differ from what would be expected due to chance.

Joint analyses, one QTL with and without population interaction: The results from the joint analyses are presented in Table 4. Estimated positions of a QTL and *F*-ratios are given as in Table 3. Distributions of the test statistic for all three traits are plotted in Figure 2. Estimated additive effects were obtained from back conversion of the effects estimated in standard deviations. The same additive effect on the standardized scale was used for all populations if the interaction model was not significantly better than the model with no population interaction. The interaction model was significantly better for FAT; therefore, the additive effects used to calculate the effect of the Large White allele were different for each population.

The joint analysis of BWT produced a peak in the *F*-ratio of 9.6 at 85 cM along the chromosome. This was significant at a genome-wide level, despite the fact that only the French data had significant evidence for an effect on BWT in the single-population analyses. The interaction with population was not significant, so the estimated additive effect was not significantly different between populations ($P = 0.16$), with an estimate of 0.15 residual standard deviations, equating to an additive effect of 21–35 g, depending on the population.

The peak *F*-ratios for GRE and FAT in the joint analysis were substantially larger than that for BWT, consistent with the fact that more individual populations had evidence for QTL effects. For GRE the estimated QTL effect did not differ significantly between populations ($P = 0.12$), with an estimate of 0.32 residual standard deviations. This equates to an estimated additive effect that varied from 11.9 g/day in the Swedish population to 20.6 g/day in the British population.

Analyses of FAT produced evidence of significant differences between populations ($P = 0.002$). The estimated QTL effect was not significantly different from 0 in US, Dutch, and German Meishan populations but in other populations the estimated additive effect was as high as −0.75 residual standard deviations (−2.57 mm in Swedish population). Estimates of the position of a QTL were very similar for all three traits (85, 81, and 86 cM for BWT, GRE, and FAT, respectively). Dominance effects were not significantly different from zero for all traits.

For both GRE and FAT the beneficial alleles (low fat, high growth) were from a commercial origin with the undesirable effects always associated with the Meishan or wild boar breeds.

Joint analyses, one QTL with breed interaction: Only the analysis of FAT indicated a significant difference ($P = 0.007$) of the estimated QTL effect between the wild-boar- and Meishan-derived populations. The effect of the QTL in wild boar populations was −0.61 ± 0.10 residual standard deviations (Sweden, −2.08 mm; Germany, −1.87 mm) and within Meishan populations −0.23 ± 0.04 residual standard deviations (Britain, −1.05 mm; France, −0.74 mm; US, −1.25 mm; Germany, −1.07 mm; Netherlands, −0.62 mm). There was no significant evidence for a dominance effect for any of the three traits.

Breed analyses, one QTL: The results analyzing the Meishan and wild boar populations in two separate groups are presented in Table 5. In the Meishan analyses the estimated positions of QTL are similar to those calculated in the joint analyses. Only the analysis of BWT produced evidence for significantly different effects between populations ($P = 0.030$), although the interaction of QTL and population approached significance for both GRE and FAT.

The analyses of the data from wild-boar-derived populations did not produce any evidence for a QTL affecting birth weight. The results of the analyses for FAT were similar to those produced from the joint analyses and

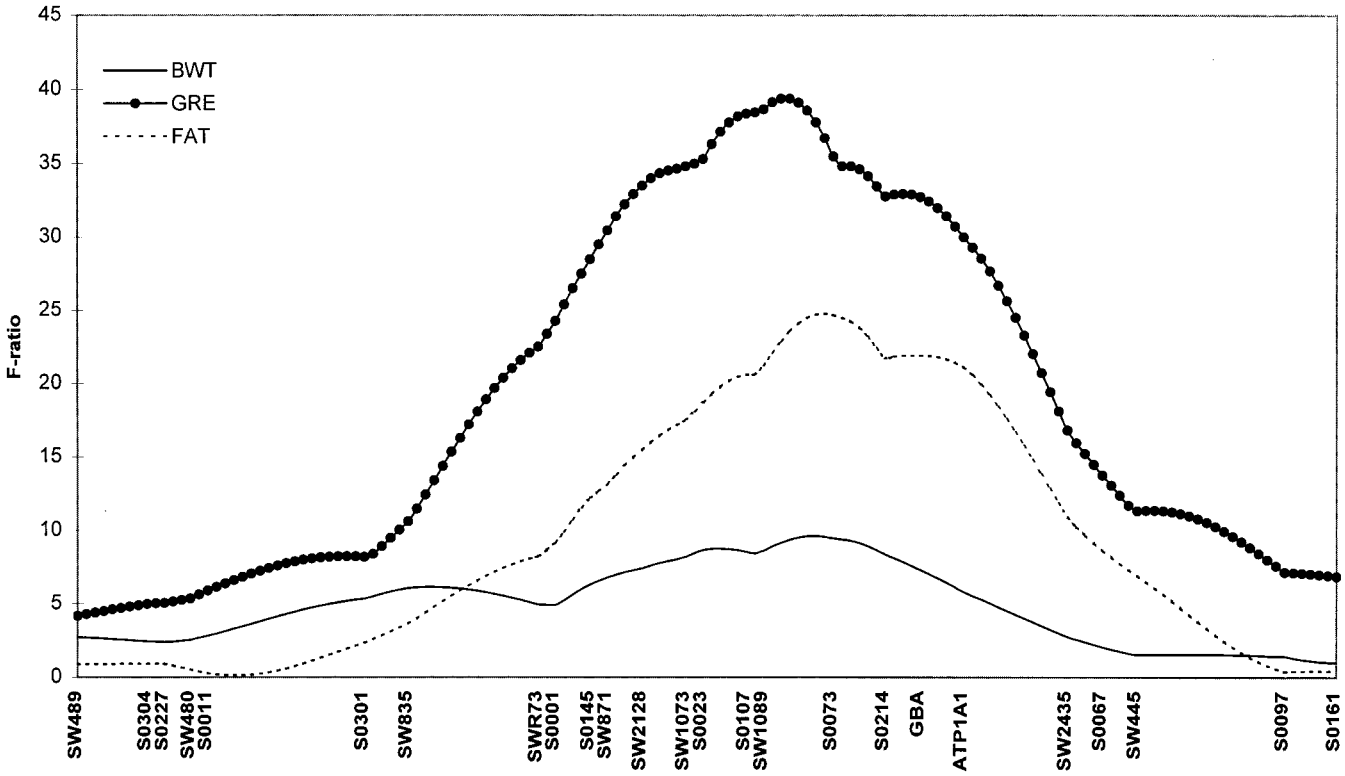

Figure 2.—Distribution of the test statistics across the chromosome for BWT, GRE, and FAT from the joint analyses fitting one QTL of constant effect in all populations. Note that some markers have been omitted from the *x* axis for clarity.

the Meishan group analyses with respect to estimated QTL position; however, the estimated additive effects were larger for the wild boar populations. The results for GRE indicated a QTL at 60 cM compared with 80 cM from the joint and Meishan analyses. Also, the estimated effects were smaller compared to the Meishan studies. The interaction with population did not significantly improve the model for any of the traits.

Two QTL: The two-QTL model for GRE placed QTL at 10 and 80 cM. This was not a significant improvement on the one-QTL model ($P = 0.12$). The estimated additive effects of the two QTL were 0.07 residual standard deviations with a standard error of 0.04 and 0.30 residual standard deviations with a standard error of 0.04.

Confidence intervals: The confidence intervals for GRE are presented in Table 6. The joint analysis produced a smaller confidence interval than all other populations with the exception of the British data. All confidence intervals shared a common region (63–84 cM). Four of the populations did not include the 0- to 50-cM region within the 95% confidence interval.

DISCUSSION

In this study we have undertaken a joint analysis of data coming from seven different F_2 populations produced by six different research groups. This QTL study includes data on almost 3000 measured and genotyped animals and is the largest F_2 study in livestock of which we are aware. The study focused on chromosome 4, for which there was substantial prior evidence that QTL would be detected, and dealt with traits for which there were homologues in all studies.

A significant QTL effect for BWT was found only in the French population; no significant effect was detected in the wild boar population or any of the other Meishan populations. Despite this, the overall QTL effect, estimated under the assumption that the wild boar and the Meishan were fixed for one allele and all commercial breeds were fixed for a second allele, was significant. There was no significant evidence that the QTL effect differed between populations. When the data were split into Meishan- and wild-boar-derived populations, the overall QTL was significant in Meishan-derived populations but there was no evidence of an effect in wild-boar-derived populations. Furthermore, there was some evidence of significant differences in the estimated effect of a QTL between populations that were Meishan derived ($P = 0.03$; Table 5). The only population that provides some support (*i.e.*, similar effect in a similar position) for the large effect found in the French population is that from The Netherlands. The most parsimonious explanation of these results would seem to be that there is a real QTL present in

TABLE 5

Results from the separate analyses of the Meishan and wild boar data

Trait	BWT (g)	GRE (g/day)	FAT (mm)
Meishan			
F-ratio	10.1**	33.1***	12.4***
Position	82	81	87
F (Int *vs.* no QTL)	3.7	8.5	4.7
F (Int *vs.* no Int)	2.1	1.8	1.7
P (Int *vs.* no Int)	0.030	0.058	0.073
Effect (SE)			
FR	46 (9)	19.8 (2.5)	−0.65 (0.13)
GB	−12 (15)	20.1 (2.5)	−0.93 (0.19)
D (ms)	−4 (20)	16.1 (2.0)	−0.95 (0.19)
US	30 (23)	17.0 (2.1)	−1.10 (0.22)
NL	20 (11)	17.2 (2.1)	−0.55 (0.11)
Wild boar			
F-ratio	1.0	9.8**	17.7***
Position	130	60	82
F (Int *vs.* no QTL)	1.3	5.8	9.5
F (Int *vs.* no Int)	1.4	1.9	1.2
P (Int *vs.* no Int)	0.238	0.155	0.294
Effect (SE)			
SW	−16 (13)	13.5 (3.0)	−1.94 (0.32)
D (wb)	−20 (16)	14.4 (3.3)	−1.74 (0.29)

* Suggestive significance; ** 5% genome-wide significance; *** 1% genome-wide significance.

For each trait in each population, the estimated QTL position is given with the *F*-ratio at that position. The effects are calculated by the residual standard deviation multiplied by the effect of the allele from the commercial breed. The same additive effect for all populations is used if the interaction model is not significantly better than the model with no population interaction.

some of the Meishan-derived populations. Differences between studies could then reflect both the samples of imported Meishan animals used, as well as differences between breeds to which they were crossed. For these relatively small QTL effects, even a study as large as this lacks the power to find significant differences between populations in the context of some of the models fitted.

There is strong evidence for a QTL effect for growth rate (GRE). Although the QTL was not significant in all the individual populations, the joint analysis was highly significant. Furthermore, the estimated effect did not differ significantly between breeds or populations and the position estimate is reasonably consistent between individual population analyses and the overall analyses. Given the quite wide range of end weights for the growth period (75–110 kg; Table 2), it is perhaps surprising that no significant differences were found between populations. However, there is no apparent association between the estimated QTL effect (Table 3) and the end weight.

TABLE 6

Confidence intervals produced by the bootstrap method for GRE

Population	95% Confidence interval (cM)	Size (cM)
Joint	63–97	34
FR	23–106	83
GB	56–84	28
D (ms)	56–102	46
US	51–144	93
NL	7–122	115
SW	36–142	106
D (wb)	0–140	140

For each individual population and the joint analysis the 95% confidence interval and its size in centimorgans are given.

The analyses of subcutaneous fat depth data (FAT) suggest the presence of a QTL in both Meishan- and wild-boar-derived populations. The populations with significant evidence for a QTL affecting FAT all located the QTL within a similar region. The results from the interaction analyses suggest this QTL has significantly different effects in the wild-boar- and Meishan-derived populations, with the effect in the wild boar significantly larger than the effect observed in the Meishan populations. The effect is not significantly different between populations of the same type, although the interaction for Meishan-derived populations approached significance ($P = 0.073$). One possible explanation for these results is that there are at least three alleles at a locus influencing FAT, one in commercial breeds and two resulting in differing amounts of additional subcutaneous fat in wild boar and Meishan breeds, respectively. However, several important factors differed between the

studies, such as different measures contributing to FAT, differing feeding regimens, and differing weights at which FAT was measured. Thus a conclusion that the wild boar and Meishan differ should be treated cautiously until further evidence is available (*e.g.*, from a QTL study in a Meishan crossed with wild boar population). The existence of a QTL affecting FAT has been confirmed by analyzing subsequent backcross generations of the Swedish population (Marklund *et al.* 1999).

The least squares mapping method (Haley and Knott 1992; Haley *et al.* 1994) was used in this study because its relative simplicity and speed of calculation are important with approaching 3000 animals and 429 F_2 families and other fixed effects and covariates to be included in the model. The analysis assumed that breeds were fixed for QTL alleles (*i.e.*, there was no within-breed segregation). Our exploratory analyses of the British and French data (Walling *et al.* 1998; G. A. Walling, P. M. Visscher and (C. S. Haley, unpublished data) found no substantial evidence of within-line segregation and so this assumption seems justified. Models for the combined analyses also grouped Large White, Landrace, Piétrain, Duroc, and Hampshire together as commercial breeds. If these breeds have different QTL alleles, this would be expected to be detected as an interaction between the population and the QTL effect. We have seen little evidence for such interactions in these analyses, although these results could be consistent with a model in which any differences between the QTL alleles in different commercial breeds are relatively small compared to the difference between commercial and other breeds.

The benefits to the joint analysis are relatively easy to see despite the fact that the data do not provide the definitive explanation to effects present on porcine chromosome 4. This is to our knowledge the largest F_2 QTL mapping data set ever analyzed for livestock. One main advantage is that the evidence for a particular QTL can be substantially increased with the extra information. This is apparent from comparing *F*-ratios from the single-population analyses to those produced from the joint analysis of the same trait. For FAT and GRE the *F*-ratio in the joint analysis is substantially higher than that from the single populations. This has a subsequent effect on the confidence intervals, which are typically smaller in the joint analysis for all populations with the exception of the British data.

Although a combined analysis of data has advantages, it has problems and limitations also. We have combined the marker data to produce a consensus map of chromosome 4. We met no substantial problems in doing this for these data, despite the fact that there was limited overlap between the markers used in different populations. However, differences in the map length between populations, especially where the magnitude of the difference varies along the chromosome, may contribute noise to the estimated positions of QTL. In addition, there was variation in traits measured and environmental conditions of different populations. Ideally all populations would have measured the same traits and genotyped for the same markers but this proves very difficult in practice. As far as the markers are concerned, consensus maps were not available when these trials were initiated and groups tended to utilize markers they developed or with which they had experience. With the development of consensus maps and distributed primer sets it has now become much easier to select markers that are also used by others. However, markers will vary in the information they provide on different populations and so it would never be possible to completely standardize the marker choice. As far as traits are concerned, husbandry and commercial conditions differ between countries and it is only natural that the projects are established to replicate testing procedures within that country. This explains the heavier slaughter weights in the American populations (110 kg) and comparatively lower weights achieved in European populations ($\sim$80 kg). Thus although it may be possible to standardize markers and trait measurements to some extent, this can never be done completely. Hence, environmental differences and other factors will always have to be considered in studies such as these and may contribute to differences between populations in estimated QTL parameters.

We have demonstrated the use of combined analysis of data from pig populations, but the principles could be very usefully applied to other species. Information for QTL mapping is often difficult or expensive to collect and many studies lack sufficient individuals to provide adequate power to detect any but the largest QTL. The cost of genotyping and collecting phenotypic data is often prohibitive for many studies, and so combining data could substantially benefit research.

We have demonstrated joint analyses achieved by combining raw data from different studies. Availability of the raw data doubtlessly gives optimum flexibility to the combined analyses; however, obtaining access to raw data may often be difficult or impractical. Without access to raw data, meta-analysis of published results may be a powerful and informative approach (Allison and Heo 1998). For QTL analyses performed by interval mapping, one approach to meta-analysis is given by the additive nature of log-likelihood test statistics obtained from the analytical approach. An example of this is demonstrated in Figure 3, where the summed test statistics from analysis of growth rate (GRE) from individual populations are compared with the joint analysis with population interaction and the standard joint analysis. In the case of these results, the summation of test statistics is achieved by adding the *F*-ratio produced by each individual population at a set position. This is repeated across the whole chromosome to create the distribution of the summed test statistics. Note that in the case of the *F*-ratio test statistics, it is necessary to standardize

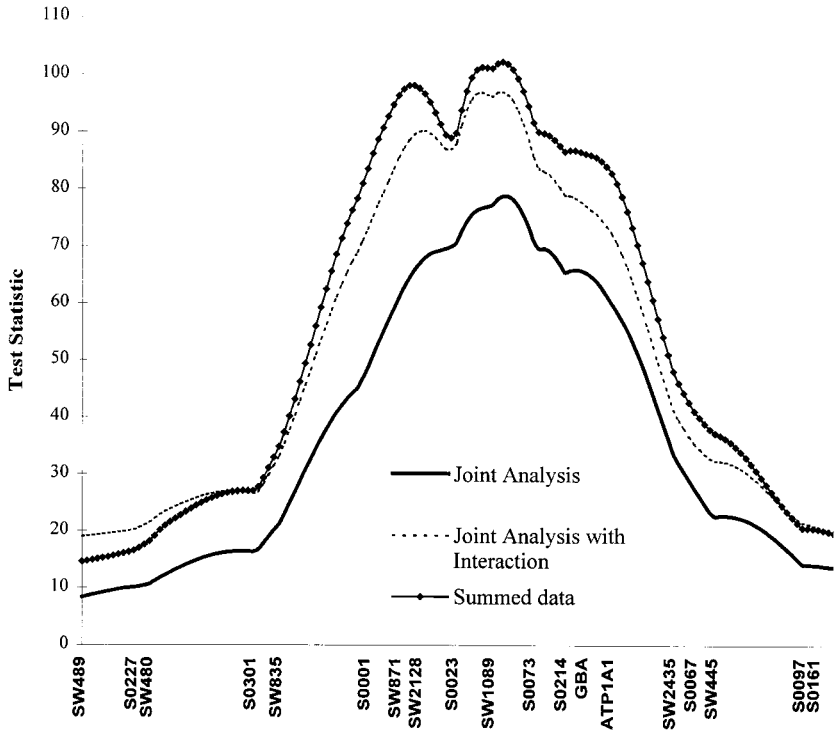

Figure 3.—Comparison of alternative methods of combining data using the example of GRE. Test statistics were standardized for degrees of freedom between different methods. Note that some markers have been omitted from the *x* axis for clarity.

for the degrees of freedom, *e.g.*, convert to approximate log-likelihood ratio test statistic by multiplication by the numerator's degrees of freedom.

The three curves on Figure 3 are obviously very similar, but they differ to some extent because the models that underlie them differ. The difference between the lines for the joint analysis and the joint analysis with population interaction exists because the interaction model allows the estimated QTL effect to vary between populations. The difference between the lines for the interaction model and the summed test statistics is due to the summed data allowing residual variance to vary between populations (the joint analysis with interaction assumes a common residual variance). The process of summing the test statistics was facilitated in our case by the fact that all analyses were performed using a common consensus map of markers. In practice it would usually be necessary to scale results from different studies to a consensus map.

It would be beneficial for those studying similar effects in other populations if results were reported so other studies could easily combine their data without reporting test statistics every centimorgan. One method of achieving this could be the reporting of test statistics and estimated regression coefficients of markers from the regression of phenotype on marker type. Using the equations of Whittaker *et al.* (1996), it would be possible to recreate the test statistic across the chromosome and the data could then be combined, *e.g.*, adding test statistics at equivalent points.

This work has demonstrated that combining data can substantially improve the resolution of QTL mapping. The concept of joint analysis could benefit many projects involved in genome analysis and provide the necessary confirmation of effects seen in an individual population. As the information required for joint analysis can be extracted from reported results, joint analysis can be used without inconveniencing different groups, providing the data are reported in a suitable form. This relatively simple analysis provides an important step for future genome analysis.

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