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JOINT QTL ANALYSIS OF THREE CONNECTED F_2-CROSSES IN PIGS

Dissertation
Zur Erlangung des Grades eines Doktors
der Agrarwissenschaften

vorgelegt

der Fakultät Agrarwissenschaften

von

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aus Nürtingen

2011

Die vorliegende Arbeit wurde am 30.März 2012 von der Fakultät Agrarwissenschaften der Universität Hohenheim als “Dissertation zur Erlangung des Grades eines Doktors der Agrarwissenschaften” angenommen.

Tag der mündlichen Prüfung:	16. Mai 2012
Prüfungsvorsitzender:	Prof. Dr. Dr. h.c. R. Mosenthin
1.Prüfer, Berichterstatter:	Prof. Dr. J. Bennewitz
2.Prüfer, Mitberichterstatter:	Prof. Dr. N. Reinsch
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CONTENT

GENERAL INTRODUCTION

Mapping Quantitative Trait Loci (QTL) has received considerable attention in livestock genetic research over the last two decades. Knowledge of the location, the mode of inheritance and the size of effects of QTL contribute to a deeper understanding of the genetic architecture of quantitative or complex traits (Hill, 2010). Furthermore, mapped QTL were envisaged for use in so-called marker assisted selection programs, MAS (Meuwissen and Goddard, 1996), although this selection scheme was only implemented in few cases (Dekkers, 2004).

Before the era of genomics started, microsatellites were usually used as genetic markers for QTL mapping. In dairy cattle, half-sib designs based on existing paternal half sibs are often employed (Weller et al., 1990). In pigs, F_2-crosses were frequently established from divergently selected founder breeds (Rothschild et al., 2007). Usually, the sizes of these F_2-experiments are in the range of 300 individuals, which is too small to obtain sufficient statistical power to map QTL precisely. One large F_2-experiment was set up in the 1990s at the University Hohenheim (Geldermann et al., 2003). Three F_2-crosses from three genetically different founder breeds (Meishan, Pietrain and European Wild Boar) with almost 1000 individuals were genotyped and phenotyped for around 50 quantitative traits. Each cross was analysed separately and more complex modes of inheritance were ignored. However, it was shown by several researchers that a combined analysis of several QTL experiments can boost statistical power (Walling et al. 2004; Bennewitz et al., 2004). Additionally, the mode of inheritance is sometimes not restricted to additive and dominant gene action. Epistasis (Carlborg and Haley, 2004) and imprinting (Boysen et al., 2010) should also be considered when mapping QTL.

The overall aim of this thesis was the joint analysis of the three F_2-crosses of Geldermann et al. (2003) with more appropriate statistical models. In **CHAPTER ONE** a statistical model tailored to jointly analyse the three crosses was developed. It was adapted from plant breeding and extended to account for imprinting. This model was applied and compared to a standard QTL model. It was shown that a joint analysis led to substantial additional power and subsequently to a larger number of significant QTL with shorter confidence intervals.

Fat related traits are frequently included as a goal in pig breeding programmes and numerous QTL have been found affecting fat traits. However, most studies used fat traits defined in a rather classical way, e.g. back fat thickness or intramuscular fat. For the interpretation of QTL results and the identification of genes and pathways underlying the QTL it might be advantageous to have some trait measurements of the direct gene products. Therefore, in **CHAPTER TWO** several metabolic, enzymatic and cytological fat traits were used in addition to classical fat traits in QTL mapping. The statistical model developed in chapter one was applied. The results were interpreted across all traits and positional and functional candidate genes underlying the QTL were suggested.

Muscling and growth traits are normally included in pig breeding programmes, especially in sire line pig breeding. In **CHAPTER THREE** six growth traits and four muscling traits were analysed, using the model developed in chapter one. Numerous QTL were found and candidate genes underlying the QTL were suggested and discussed.

The thesis ends with a general discussion and a summary.

The calculation of information content for mapping additive and imprinting QTL in the joint design as well as QTL results of numerous other traits not discussed in the previous chapters are included in the appendixes.

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CHAPTER ONE

Joint QTL analysis of three connected F_2-crosses in pigs

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Published in:

Genetics Selection Evolution **(2010), 42:40-52**

ISSN: 12979686

doi:10.1186/1297-9686-42-40

Joint QTL analysis of three connected F_2-crosses in pigs

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Abstract

Background

Numerous QTL mapping resource populations are available in livestock species. Usually they are analysed separately, although the same founder breeds are often used. The aim of the present study was to show the strength of analysing F_2-crosses jointly in pig breeding when the founder breeds of several F_2-crosses are the same.

Methods

Three porcine F_2-crosses were generated from three founder breeds (i.e. Meishan, Pietrain and wild boar). The crosses were analysed jointly, using a flexible genetic model that estimated an additive QTL effect for each founder breed allele and a dominant QTL effect for each combination of alleles derived from different founder breeds. The following traits were analysed: daily gain, back fat and carcass weight. Substantial phenotypic variation was observed within and between crosses. Multiple QTL, multiple QTL alleles and imprinting effects were considered. The results were compared to those obtained when each cross was analysed separately.

Results

For daily gain, back fat and carcass weight, 13, 15 and 16 QTL were found, respectively. For back fat, daily gain and carcass weight, respectively three, four, and five loci showed significant imprinting effects. The number of QTL mapped was much higher than when each design was analysed individually. Additionally, the test statistic plot along the chromosomes was much sharper leading to smaller QTL confidence intervals. In many cases, three QTL alleles were observed.

Conclusions

The present study showed the strength of analysing three connected F_2-crosses jointly. In this experiment, statistical power was high because of the reduced number of estimated parameters and the large number of individuals. The applied model was flexible and was computationally fast.

Background

Over the last decades, many informative resource populations in livestock breeding have been established to map quantitative trait loci (QTL). Using these populations, numerous QTL for many traits have been mapped [1]. However, the mapping resolution of these studies is usually limited by the size of the population. One way to increase the number of individuals is to conduct a joint analysis of several experimental designs. In dairy cattle breeding, a joint analysis of two half-sib designs with some overlapping families has been performed by Bennewitz et al. [2] and has shown that a combined analysis increases statistical power substantially, due to the enlarged design and especially due to increased half-sib family size. In pig breeding, a joint analysis has been successfully implemented by Walling et al. [3] in which seven independent F_2-crosses have been analysed in a combined approach for one chromosome. The mapping procedure developed by Haley et al. [4] was used where some breeds are initially grouped together in order to fulfil the assumption of the line cross approach (i.e. two founder lines are fixed for alternative QTL alleles). Further examples can be found in Kim et al. [5] and Pérez-Enciso et al. [6], both using pig crosses, or in Li et al. [7] using laboratory mouse populations.

Analysing several F_2-crosses jointly could be especially useful when the founder breeds used for the crosses are the same in all the designs. This situation can occur in plant breeding, where crosses are produced from a diallel design of multiple inbred lines (e.g. Jansen et al. [8]). Although rare in livestock breeding, one example is the experiment described by Geldermann [9]. For this kind of experiment Liu and Zeng [10] have proposed a flexible multiallelic mixture model, which estimates an additive QTL effect for each founder line and a dominant QTL effect for each founder line combination. They have estimated their model by adopting maximum likelihood using an EM algorithm.

The aim of the present study was to conduct a joint genome scan covering the autosomes for three porcine F_2-crosses derived from three founder breeds. For this purpose, the method of Liu and Zeng [10] was modified in order to include imprinting effects. The effect of a combined analysis was demonstrated by comparing the results for three traits with those obtained when the three crosses were analysed separately.

Methods

Connected F_2-crosses

The experimental design is described in detail by Geldermann et al. [9] and only briefly reminded here. The first cross (MxP) was obtained by mating one Meishan (M) boar with eight Pietrain (P) sows. The second cross (WxP) was generated by mating one European wild boar (W) with nine P sows, some of which were the same as in the MxP cross. The third cross (WxM) was obtained by mating the same W boar with four Meishan (M) sows. The number of F_1-individuals in the MxP, WxP and WxM crosses was 22, 28 and 23, respectively and the the number of F_2-individuals was 316, 315 and 335, respectively. The number of sires in the F_1-generation was between two and three. The joint design was built by combining all three designs. All individuals were kept on one farm; housing and feeding conditions have been described by Müller et al. [11]. All F_2-individuals were phenotyped for 46 traits including growth, fattening, fat deposition, muscling, meat quality, stress resistance and body conformation, see [11] for further details. In this study, we investigated three traits i.e. back fat depth, measured between the 13^{th} and 14^{th} ribs, daily gain and carcass weight. The phenotypes were pre-corrected for the effect of sex, litter, season and different age at slaughtering before QTL analysis. The means and standard deviations of the observations are given in Table 1. There is substantial variation within and between crosses for all three traits. Altogether 242 genetic markers (mostly microsatellites) were genotyped, covering all the autosomes, with a large number of overlapping markers in the crosses. Both sex chromosomes were excluded from the analysis because they deserve special attention (Pérez-Enciso et al. [6]).

Table 1: Number of observations (n), mean, standard deviation (Sd), minimum (Min) and maximum (Max) of the phenotypic observations and coefficient of variation (CV).

Trait	Cross	n	Mean	Sd	Min	Max	CV
Back fat depth [mm]	MxP	316	21.96	6.94	6.7	43.3	31.59
	WxP	315	16.76	5.85	5.3	37.3	34.92
	WxM	335	31.62	8.62	6.0	54.7	27.25
	Joint	966	23.61	9.54	5.3	54.7	40.40
Daily gain [g]	MxP	316	589.49	132.03	174.0	951.0	22.40
	WxP	315	528.78	107.83	125.0	790.0	20.39
	WxM	335	456.65	94.14	143.0	741.0	20.61
	Joint	966	523.63	124.61	125.0	951.0	23.80
Carcass weight [kg]	MxP	316	76.22	14.19	42.2	109.6	18.62
	WxP	315	57.14	12.60	19.7	89.2	22.05
	WxM	335	54.75	11.71	20.8	86.8	21.38
	Joint	966	62.55	16.02	19.7	109.6	25.61

Linkage maps and information content

A common linkage map was estimated using Crimap [12]. Due to the large number of overlapping markers these calculations were straightforward. It was assumed that two founder breeds (breed *i* and *j*, with *i* and *j* being breed M, P, or W) of a single cross are divergent homozygous at a QTL, i.e. showing only genotype Q_iQ_i and Q_jQ_j, respectively. Although the three breeds in this study are outbred breeds, this assumption holds approximately, because the breeds have a very different history and are genetically divergent (see also Haley et al. [4]). Subsequently, for each F_2-individual of a certain cross four genotype probabilities $pr(Q_i^pQ_i^m)$, $pr(Q_j^pQ_i^m)$, $pr(Q_i^pQ_j^m)$ and $pr(Q_j^pQ_j^m)$ were calculated for each chromosomal position. The upper subscript denotes the parental origin of the alleles (i.e. paternal (*p*) or maternal (*m*) derived) and the lower subscript denotes the breed origin of the alleles (i.e. breed *i* or *j*). These probabilities were estimated using a modified version of Bigmap [13]. This program follows the approach of Haley et al. [4] and uses information of multiple linked markers, which may or may not be fixed for alternative alleles in the breeds. The information content for additive and imprinting QTL effects were estimated for each chromosomal position, using an entropy-based information measure as described by Mantey et al. [14]. The information content for the additive QTL effect represents the probability that two alternative QTL homozygous genotypes can be distinguished, given the individuals are homozygous. Similarly, the imprinting information content denotes the probability that two alternative

heterozygous QTL genotypes can be separated, given that the individuals are heterozygous. The information content was solely used to assess the amount of information available to detect QTL and was not used for the QTL mapping procedure.

Genetic and statistical model

On the whole, the genetic model followed the multiallelic model of Liu and Zeng [10], but was extended to account for imprinting. It is assumed that the breeds are inbred at the QTL. The genetic mean was defined as the mean of the $L = 3$ founder breeds. Considering one locus, the mean is

$$\mu = \frac{\sum_{i=1}^{L} g_{ii}}{L},$$

with g_{ii} being the homozygote genotypic value in breed i (i = M, P, and W, respectively). Now let us consider haploid populations. The mean of the breeds consisting of paternal derived and maternal derived alleles at the locus is

$$\mu^p = \frac{\sum_{i=1}^{L} g_i^p}{L} \text{ and } \mu^m = \frac{\sum_{i=1}^{L} g_i^m}{L},$$

respectively. The term g_i^p (g_i^m) denotes the genotypic value of the paternal (maternal) derived allele. The additive effect of the paternal derived and maternal derived allele is $a_i^p = g_i^p - \mu^p$ and $a_i^m = g_i^m - \mu^m$, respectively. This imposes the restrictions

$$\sum_{i=1}^{L} a_i^p = 0 \text{ and } \sum_{i=1}^{L} a_i^m = 0. \quad (1)$$

In this haploid model, putative imprinting effects will result in different haploid means. However, in a diallelic model the two haploid means are not observable, but become part of the mean as $\mu = \mu^p + \mu^m$. Thus the genetic model of the diploid F_2-population generated from the breeds i and j is as follows:

$$\begin{bmatrix} g_{ii}^{pm} \\ g_{ij}^{pm} \\ g_{ji}^{pm} \\ g_{jj}^{pm} \end{bmatrix} = \begin{bmatrix} 1 & 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 1 & 0 & 1 \\ 0 & 0 & 1 & 1 & 0 \end{bmatrix} \begin{bmatrix} a_i^p \\ a_i^m \\ a_j^p \\ a_j^m \\ d_{ij} \end{bmatrix} + \begin{bmatrix} \mu \\ \mu \\ \mu \\ \mu \end{bmatrix}, \quad (2)$$

where again the upper subscripts denote the parental origin and the lower subscripts denote the breed origin of the alleles. Putative imprinting effects will result in $a_i^p \neq a_i^m$. This genetic model was used to set up the statistical model. We used the notation of Liu and Zeng [10] for comparison purposes.

$$y_{ijk} = cross_{ij} + (z^p_{ijk,i}\mathbf{w}^p_{ijk,i} + z^m_{ijk,i}\mathbf{w}^m_{ijk,i} + z^p_{ijk,j}\mathbf{w}^p_{ijk,j} + z^m_{ijk,j}\mathbf{w}^m_{ijk,j})\mathbf{a} + z^{pm}_{ijk}\mathbf{w}^{pm}_{ijk}\mathbf{d} + e_{ijk} \quad (3)$$

where y_{ijk} is the phenotypic observation of the kth individual in the F_2-cross derived from breed i and j. The term $cross_{ij}$ denotes the fixed effect of the F_2-cross. It was included in the model (and not in the model for the pre-correction of the data for other systematic effects as described above), because it contains a part of the genetic model (i.e. the mean). The term e_{ijk} is a random residual with heterogeneous variance, i.e. $e_{ijk} \sim N(0, \sigma^2_{ij})$. Vector **a** contains the additive effects ($a_1^p, a_1^m, ...a_L^p, a_L^m$) and vector **d** contains the dominance effects ($d_{1,2}$, $d_{1,3}$, …, $d_{(L\text{-}1),L}$). The four **w** terms are row vectors of length 2*L with one element equal to one and the other elements equal to zero. Each **w** term indicates one of the four possible additive effects in **a** that could be observed in the F_2-individual based on pedigree data. For example, $w^p_{ijk,i}$ denotes the putative allele in offspring *ijk* (indicated by first lower subscript *ijk*) inherited paternally (indicated by upper subscript *p*) from line *i* (indicated by second lower subscript *i*). The four z terms are scalars and are either zero or one. They indicate if the offspring inherited the corresponding allele from the corresponding parent. For each offspring these four terms sum up to two. Similarly, w^{pm}_{ijk} is a row vector of length L, indicating which dominance effect could be possible in the offspring based on pedigree data. The scalar z^{pm}_{ijk} is one if the offspring is heterozygous at the QTL and zero otherwise. The true z terms were unknown and therefore calculated from the four estimated QTL-genotype probabilities at each chromosomal position. For example, the term $z^p_{ijk,i}$ was set equal to $pr(Q_i^p Q_i^m) + pr(Q_i^p Q_j^m)$. The dominance term ($z^{pm}_{ijk}$) was the sum of the two heterozygous genotype probabilities. The statistical model was a multiple linear regression. The residual variance was assumed to be heterogeneous.

In order to avoid an over-parameterisation due to the restrictions shown in (1), the genetic model (2) was re-parameterised taking the restrictions in (1) into account, as shown in Appendix. The final regression was also re-parameterised taking these restrictions into

account. Hence, in fact only 2*L-2 = 4 additive effects were estimated (i.e. $\hat{a}_i^p, \hat{a}_i^m, \hat{a}_j^p, \hat{a}_j^m$). The estimated paternal additive effects of the breeds were $\hat{a}_M^p = \hat{a}_i^p$, $\hat{a}_P^p = \hat{a}_j^p$, and $\hat{a}_W^p = -(\hat{a}_i^p + \hat{a}_j^p)$, respectively, where the lower subscripts M, P and W denote the three breeds. The same holds true for the maternal additive effects. The combined mendelian additive QTL effects for the three breeds were calculated as $\hat{a}_M = \hat{a}_i^p + \hat{a}_i^m$, $\hat{a}_P = \hat{a}_j^p + \hat{a}_j^m$, and $\hat{a}_W = -(\hat{a}_i^p + \hat{a}_i^m + \hat{a}_j^p + \hat{a}_j^m)$.

The model was fitted every cM on the autosomes by adapting the z terms accordingly. The test statistic was an F-test; the F-values were converted into LOD-scores as $LOD \approx (np * F)/(2 * \log(10))$, with np being the number of estimated QTL effects [14], i.e. np = 7 (four additive and three dominance effects).

When imprinting is not accounted for, the models (2) and (3) reduce to the proposed model of Liu and Zeng [10]. In this case, L - 1 = 2 additive effects are estimated. In this study, this was also solved by using multiple linear regressions with heterogeneous residual variances.

Hypothesis testing

The highest test-statistic was recorded within a chromosome-segment (for the definition of a chromosome-segment see the next section). The global null hypothesis was that at the chromosomal position with the highest test statistic, every estimated parameter in **a** and **d** is equal to zero. The corresponding alternative hypothesis was that at least one parameter was different from zero. The 5% threshold of the test statistic corrected for multiple testing within the chromosome-segment was obtained using the quick method of Piepho [15]. Once the global null hypothesis was rejected, the following sub-hypotheses were tested at significant chromosomal positions by building linear contrasts.

Test for an additive QTL:

$H_0: a_i^p + a_i^m = 0$ and $a_j^p + a_j^m = 0$, $H_1: a_i^p + a_i^m \neq 0$ and / or $a_j^p + a_j^m \neq 0$.

The test statistic was an F-test with two degrees of freedom in the numerator.

Test for dominance at the QTL:

$H_0: d_{ij} = 0$, $H_1: d_{ij} \neq 0$.

The test statistic was an *F*-test with three degrees of freedom in the numerator.

Test for imprinting at the QTL:

H_0: $a_i^p = a_i^m$ and $a_j^p = a_j^m$, H_1: $a_i^p \neq a_i^m$ and / or $a_j^p \neq a_j^m$.

The test statistic was an *F*-test with two degrees of freedom in the numerator. The mode of imprinting (either paternal or maternal imprinting) at the QTL with significant imprinting effects was assessed by comparing the paternal and maternal effect estimates.

The test of the three sub-hypotheses resulted in the three error probabilities p_{add}, p_{dom}, and p_{imp} for additive, dominance and imprinting QTL, respectively. Note that if the global null hypothesis was rejected, at least one of the three sub-null-hypotheses had to be rejected as well. Therefore, correction for multiple testing was done only for the global null hypothesis, and for the sub-null-hypothesis, the comparison-wise error probabilities were reported.

Finally, the number of QTL alleles that could be distinguished based on their additive effects was assessed. This was done by testing the segregation of the QTL in each of the three crosses, considering only additive mendelian effects (i.e. ignoring imprinting and dominance). The corresponding test was:

H_0: $a_i^p + a_i^m = a_j^p + a_j^m$, H_1: $a_i^p + a_i^m \neq a_j^p + a_j^m$.

Once again an *F*-test was used and was applied for each of the three crosses. If the QTL segregated between two (three) crosses the number of QTL alleles was two (three). Note that it was not possible that a QTL segregated solely in one cross.

Confidence intervals and multiple QTL

For each significant QTL, a confidence interval was calculated using the one LOD-drop method mentioned in Lynch and Walsh [16]. The lower and upper bounds were then obtained by going from the lower and upper endpoints of the one LOD-drop region to the next left and next right marker, respectively. This procedure worked against the anti-conservativeness of the one LOD-drop off method. The anti-conservativeness was shown by Visscher et al. [17].

The procedure to include multiple QTL in the model is recursive and proceeds as follows. Initially, the genome was scanned and the 5% chromosomes-wise thresholds were estimated. Next the QTL with the highest test statistic exceeding the threshold was included as a cofactor in the model and the genome was scanned again, but excluding the positions within the

confidence interval of this QTL. This was repeated until no additional significant QTL could be identified. In each round of cofactor selection, the question of whether the test statistic of previously identified QTL remained above their significance threshold levels was assessed; a QTL was excluded from the model if no longer significant. This can happen if some linked or even unlinked QTL co-segregate by chance (e.g. de Koning et al. [18]) and the strategy used here accounts for this co-segregation. The thresholds were calculated for chromosomes without having a QTL as a cofactor in the model considering the whole chromosome (i.e. 5% chromosome-wise thresholds). If, however, a QTL on a chromosome was already included as a cofactor, the thresholds were estimated for the chromosome segment spanned by a chromosomal endpoint and the next bound of the QTL confidence interval (i.e. 5% chromosome-segment-wise). In case more than one QTL was included as a cofactor on a chromosome, a chromosome-segment between two QTL was spanned by the two neighbouring bounds of the confidence intervals and the threshold was calculated for this chromosome segment. By defining chromosome-segments in this way, multiple QTL on one chromosome were considered. The significance thresholds were determined for the regions on the chromosomes that were scanned for QTL.

Separate analysis of three crosses

In the study of Geldermann et al. [9], the crosses were analysed separately, but without modelling imprinting. Therefore, in order to show the benefit of the joint analysis, the crosses were analysed again separately, but accounting for imprinting. The following standard model was applied:

$$y_{ijk} = \mu + a * p_a + d * p_d + imp * p_{im} + e_{ijk}, \qquad (4)$$

where μ is the mean of the F_2-offpring of the cross, $p_a = pr(Q_i^p Q_i^m) - pr(Q_j^p Q_j^m)$, $p_d = pr(Q_i^p Q_j^m) + pr(Q_j^p Q_i^m)$, and $p_{im} = pr(Q_i^p Q_j^m) - pr(Q_j^p Q_i^m)$. The terms *a*, *d*, and *im* are the regression coefficients, representing the additive, dominance, and imprinting effects, respectively. The test statistic was an *F*-test; LOD scores were obtained as described above, but using *np* = 3. Chromosome-segment-wise 5% threshold values were obtained again using the quick method explained earlier. Multiple QTL were considered as described above.

Results

The marker order of the estimated linkage map (see Additional file 1) is in good agreement with other maps. The average information content for additive and imprinting effects was

high (about 0.868 and 0.752, respectively, averaged over all individuals and chromosomal positions). This indicated that informative markers were dense enough to detect imprinting effects (which requires a higher marker density [14]).

The results of the joint design (obtained with model (3)) for the traits back fat depth, daily gain and carcass weight are shown in Tables 2, 3 and 4, respectively, and of the separate analysis of the three crosses (obtained with model (4)) are shown in Table 5.

Table 2: QTL results from the joint design and back fat

SSC	Position	CI [a]	*F*-value	p_{add} [b]	p_{dom} [c]	p_{imp} [d]	Order of effects [e]
1	90	[59.3; 95.8]	3.11	0.0195	0.0762	0.1062	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
1	144	[126.3; 149.6]	6.81	<0.0001	0.0889	0.2779	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
1	179	[149.6; 209.1]	2.80	0.0101	0.1010	0.5290	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
2	13	[0.0; 39.9]	5.01	0.0058	0.5031	<0.0001	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
2	77	[68.0; 81.0]	5.79	<0.0001	0.1947	0.3441	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
6	100	[96.4; 101.2]	6.46	<0.0001	0.0275	0.0587	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
7	83	[75.5; 100.9]	5.81	<0.0001	0.0593	0.0422	$\hat{a}_W > \hat{a}_M = \hat{a}_P$
11	83	[61.0; 93.3]	2.77	0.0094	0.1511	0.0939	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
12	58	[0.0; 84.1]	3.37	0.2599	0.0006	0.2458	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
13	56	[39.2; 81.2]	2.34	0.3950	0.0134	0.1595	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
14	51	[27.5; 60.7]	3.05	0.0107	0.0332	0.0802	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
17	74	[43.6; 97.9]	2.26	0.0199	0.9068	0.0267	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
18	27	[10.9; 43.6]	4.38	<0.0001	0.0251	0.2384	$\hat{a}_M = \hat{a}_P > \hat{a}_W$

[a] confidence interval (CI); [b] comparison-wise error probability for additive effects; [c] comparison-wise error probability for dominant effects; [d] comparison-wise error probability for imprinting effects; [e] $\hat{a}_P$ estimated effect of Pietrain breed, $\hat{a}_M$ estimated effect of Meishan breed, $\hat{a}_W$ estimated effect of the wild boar breed

Table 3: QTL results from the joint design and daily gain

SSC	Position	CI [a]	*F*-value	p_{add} [b]	p_{dom} [c]	p_{imp} [d]	Order of effects [e]
1	58	[25.4; 77.3]	3.27	0.0001	0.1850	0.6335	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
1	134	[126.3; 141.7]	6.15	<0.0001	0.1376	0.1203	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
2	8	[0.0; 39.9]	3.17	0.0058	0.0173	0.8928	$\hat{a}_P = \hat{a}_W > \hat{a}_M$
3	58	[50.8; 74.0]	5.39	0.0006	0.0008	0.0241	$\hat{a}_P = \hat{a}_W > \hat{a}_M$
4	93	[85.6; 98.1]	5.15	<0.0001	0.5892	0.7868	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
5	128	[92.2; 150.4]	2.95	0.4389	0.8924	0.0001	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
6	91	[80.0; 112.0]	2.93	0.0110	0.0647	0.1012	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
6	202	[177.9; 235.5]	2.94	0.0441	0.0161	0.1780	$\hat{a}_W > \hat{a}_M = \hat{a}_P$
7	42	[24.8; 94.4]	2.65	0.0080	0.5892	0.0261	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
8	8	[0.0; 34.0]	4.20	<0.0001	0.5782	0.0363	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
9	90	[80.0; 110.1]	2.86	0.0018	0.5195	0.1961	$\hat{a}_W > \hat{a}_M = \hat{a}_P$
9	194	[187.4; 194.6]	3.29	0.0778	0.0011	0.3357	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
10	53	[30.6; 74.1]	2.98	0.6023	0.0044	0.0509	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
15	67	[52.5; 99.4]	2.99	0.0038	0.0655	0.4120	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
16	87	[69.4; 98.0]	3.14	0.2405	0.0043	0.0676	$\hat{a}_M = \hat{a}_P = \hat{a}_W$

[a] confidence interval (CI); [b] comparison-wise error probability for additive effects; [c] comparison-wise error probability for dominant effects; [d] comparison-wise error probability for imprinting effects; [e] $\hat{a}_P$ estimated effect of Pietrain breed, $\hat{a}_M$ estimated effect of Meishan breed, $\hat{a}_W$ estimated effect of the wild boar breed

Table 4: QTL results from the joint design and carcass weight

SSC	Position	CI [a]	*F*-value	p_{add} [b]	p_{dom} [c]	p_{imp} [d]	Order of effects [e]
1	89	[77.3; 104.1]	7.94	<0.0001	0.7482	0.0385	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
2	76	[70.6; 81.0]	5.55	<0.0001	0.0143	0.2408	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
3	0	[0.0; 35.9]	3.34	0.0001	0.1644	0.5312	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
3	58	[50.2; 74.0]	3.01	0.0489	0.0064	0.3611	$\hat{a}_P = \hat{a}_W > \hat{a}_M$
4	73	[62.1; 81.0]	6.00	<0.0001	0.2317	0.6112	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
4	97	[87.6; 107.7]	2.64	0.0016	0.3586	0.1014	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
5	120	[110.0; 150.4]	3.05	0.0216	0.7526	0.0022	$\hat{a}_W > \hat{a}_M = \hat{a}_P$
6	87	[80.0; 94.4]	4.38	0.0006	0.0105	0.0800	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
7	36	[0.0; 50.0]	2.60	0.1441	0.0243	0.0415	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
7	59	[36.3; 73.3]	3.63	0.0003	0.0623	0.4030	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
8	13	[0.0; 34.0]	4.80	<0.0001	0.3863	0.0822	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
8	127	[110.1; 151.8]	2.99	0.0191	0.0088	0.6977	$\hat{a}_P = \hat{a}_W > \hat{a}_M$
10	59	[30.6; 74.1]	2.69	0.9783	0.0346	0.0085	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
12	86	[64.5; 109.8]	2.53	0.0070	0.2919	0.0902	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
14	93	[60.7; 105.1]	2.98	<0.0001	0.9244	0.8026	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
16	0	[0.0; 21.2]	3.62	0.4887	0.0438	0.0010	$\hat{a}_M = \hat{a}_P = \hat{a}_W$

[a] confidence interval (CI); [b] comparison-wise error probability for additive effects; [c] comparison-wise error probability for dominant effects; [d] comparison-wise error probability for imprinting effects; [e] $\hat{a}_P$ estimated effect of Pietrain breed, $\hat{a}_M$ estimated effect of Meishan breed, $\hat{a}_W$ estimated effect of the wild boar breed

Table 5: QTL results from the three single crosses (MxP, WxP, WxM) for the three traits

Cross	Trait	SSC	Position	CI	
MxP	Back fat depth	2	52	[0.0;	78.3]
		6	97	[80.0;	98.3]
		6	100	[98.3;	101.2]
		6	104	[101.2;	124.9]
		12	4	[0.0;	51.0]
WxP		1	135	[126.3;	149.6]
		7	47	[0.0,	73.3]
WxM		1	144	[126.3;	149.6]
		2	78	[52.9;	81.0]
MxP	Daily gain	3	58	[50.8;	74.0]
WxP		1	60	[43.5;	77.3]
		1	90	[77.3;	119.2]
		1	133	[119.2;	141.7]
		2	67	[52.9;	96.0]
		8	0	[0.0;	18.0]
		9	194	[187.4;	194.6]
WxM		7	58	[36.3;	73.3]
		15	66	[52.5;	99.4]
MxP	Carcass weight	2	76	[70.6;	78.3]
		4	82	[27.7;	98.1]
		8	21	[0.0;	49.4]
WxP		1	62	[43.5;	77.3]
		1	133	[110.3;	141.7]
		2	68	[52.9;	81.0]
		2	90	[81.0;	115.1]
		16	0	[0.0;	21.2]
WxM		1	83	[43.5;	95.8]
		1	144	[126.3;	149.6]
		7	63	[50.0;	75.2]

For each reported QTL (i.e. showing an error probability smaller than 5% chromosome-segment-wise) the estimated QTL position, the confidence interval, and the comparison-wise error probabilities of the sub-hypothesis are given. A sub-hypothesis was declared as significant if the comparison-wise error probability was below 5%. QTL effects are often heavily overestimated due to significance testing (e.g. Göring et al. [19]). Therefore, we did not report these estimates, except for QTL showing imprinting (Table 6). Instead we reported the order of the breed QTL effects in Tables 2,3 and 4.

Thirteen QTL were found for back fat depth (see Table 2) of which 11 showed a significant additive effect, five significant dominant effects and three a significant imprinting effect. The QTL on SSC12 and SSC13 were only significant because of their dominance effects. For three QTL, three alleles could be identified based on their combined additive effect. In all

three cases the effect of the P breed allele was highest, followed by the effect of the M breed allele. For other QTL, the effect of the M breed allele was higher compared to that of the P and W breeds, whereby P and W were often the same when only two QTL alleles could be separated. Naturally, for those QTL without a significant additive effect no order of breed allele effects could be observed. For daily gain, 15 QTL were mapped of which 11 showed a significant additive, six a significant dominant and four a significant imprinting effect (Table 3). The QTL on SSC5 was only significant because of its imprinting effect and the QTL on SSC9, SSC10 and SSC16 were significant because of their dominance. For five QTL, three breed alleles could be identified and the order was always P over M over W. For the QTL with only two alleles, the alleles of breeds P and W or of P and M breeds were the same, but not for M and W breeds. For carcass weight, 16 QTL were mapped of which 13 showed a significant additive, seven a significant dominant and five a significant imprinting effect. For nine QTL, three different breed alleles could be identified and the order was always P over M over W.

Imprinting seemed to be important for these traits. When imprinting was not accounted for in the joint design, only eight, nine and nine QTL were mapped for respectively back fat depth, daily gain and carcass weight (not shown). Notably, all QTL found with the model without imprinting were also found when imprinting was considered (not shown). Imprinting was not always found in all breeds. For examples see Table 6, where estimated additive QTL effects are shown for traits with a significant imprinting effect. For example, the paternal allele effect of the P breed at the QTL for carcass weight on SSC7 was higher compared to the maternal allele effect, which pointed to maternal imprinting. This, however, was not observed in the M breed at this QTL (Table 6). The QTL on SSC3 for daily gain showed opposite modes of imprinting in the M and P breeds. Also no clear mode of imprinting could be observed for the imprinted QTL on SSC2. For the remaining QTL with imprinting effects the mode of imprinting was consistent (Table 6).

Table 6: Additive QTL effects and mode of imprinting for QTL showing significant imprinting effects: results from the joint design

Trait	SSC	Pos.	$\hat{a}_M^{p\,*}$		$\hat{a}_M^m$		$\hat{a}_P^p$		$\hat{a}_P^m$		$\hat{a}_W^p$		$\hat{a}_W^m$		Mode
Back fat depth	2	13	**1.30**	(0.65)	0.10	(0.65)	-1.18	(1.00)	0.75	(1.03)	-0.12	(1.61)	-0.85	(1.65)	nc
	7	83	**-1.28**	(0.64)	**-3.30**	(0.67)	-0.002	(0.99)	**-2.97**	(1.05)	1.28	(1.59)	**5.26**	(1.67)	pat
	17	74	**2.42**	(0.67)	-0.41	(0.70)	**3.31**	(1.11)	-1.33	(1.19)	**-5.72**	(1.74)	1.73	(1.85)	mat
Daily gain	3	58	**-24.99**	(9.52)	10.69	(9.20)	-4.67	(18.27)	**35.03**	(16.05)	29.66	(26.62)	-45.72	(24.19)	nc
	5	128	**-30.74**	(9.77)	15.29	(10.17)	-28.06	(16.38)	-2.62	(16.92)	**58.80**	(25.07)	-12.67	(25.92)	mat
	7	42	3.98	(9.42)	**34.75**	(10.14)	19.17	(15.65)	26.04	(16.81)	-23.15	(23.61)	**-60.79**	(25.47)	pat
	8	8	16.73	(10.51)	-7.26	(10.82)	**71.24**	(17.96)	3.81	(18.63)	**-87.97**	(27.2)	3.45	(28.01)	mat
Carcass weight	1	89	**6.08**	(1.36)	**3.22**	(1.30)	**10.41**	(2.33)	**10.12**	(2.23)	**-16.49**	(3.55)	**-13.33**	(3.40)	mat
	5	120	**-3.76**	(0.97)	0.01	(0.99)	**-4.36**	(1.66)	-2.10	(1.69)	**8.12**	(2.53)	2.09	(2.57)	mat
	7	36	1.07	(1.52)	2.31	(1.51)	**5.79**	(2.75)	1.22	(2.66)	-6.86	(4.04)	-3.54	(4.01)	nc
	10	59	**2.47**	(1.09)	-2.20	(1.21)	**4.59**	(1.90)	-4.01	(2.07)	**-7.06**	(2.87)	6.21	(3.17)	mat
	16	0	**2.90**	(1.05)	-1.70	(1.10)	**6.31**	(1.78)	-3.42	(1.84)	**-9.21**	(2.72)	5.11	(2.82)	mat

Significant additive effects are written in bold face; standard errors are given in parenthesis;

*upper subscript denotes parental origin (paternal or maternal derived) and lower subscript denotes breed (M, P or W); mat = maternal, pat = paternal, nc = not consistent

The results of the separate analysis of the crosses (Equation (4)) can be found in Table 5. When comparing with the results of the joint design it can be observed that the number of significant QTL is much lower in the separate analysis, even if all QTL across the three crosses are considered as separate QTL. Additionally, in the joint design it was sometimes possible to map several QTL for one trait on one chromosome. For example, on SSC1 three QTL were detected for back fat depth in the joint design, whereas only one was detected within the single crosses. A comparison of the plots of the corresponding test statistics is given in Figure 1. The plot of the joint design is much sharper and more pronounced, leading to the separation of the three QTL. This can also be found on SSC2 for the same trait (Figure 1). On the one hand, in this case two QTL were found in the joint design, but one QTL in the designs MxP and WxM (Tables 2 to 5). On the other hand, almost all QTL detected in the single designs were also found in the joint design. This can be seen when comparing the overlap of the confidence intervals of the QTL (Tables 2, 3, 4 and 5).

When selecting QTL as cofactors, every QTL remained above its significance threshold level, and thus stayed in the model. For most QTL, the test statistic increased when additional QTL were selected as cofactors.

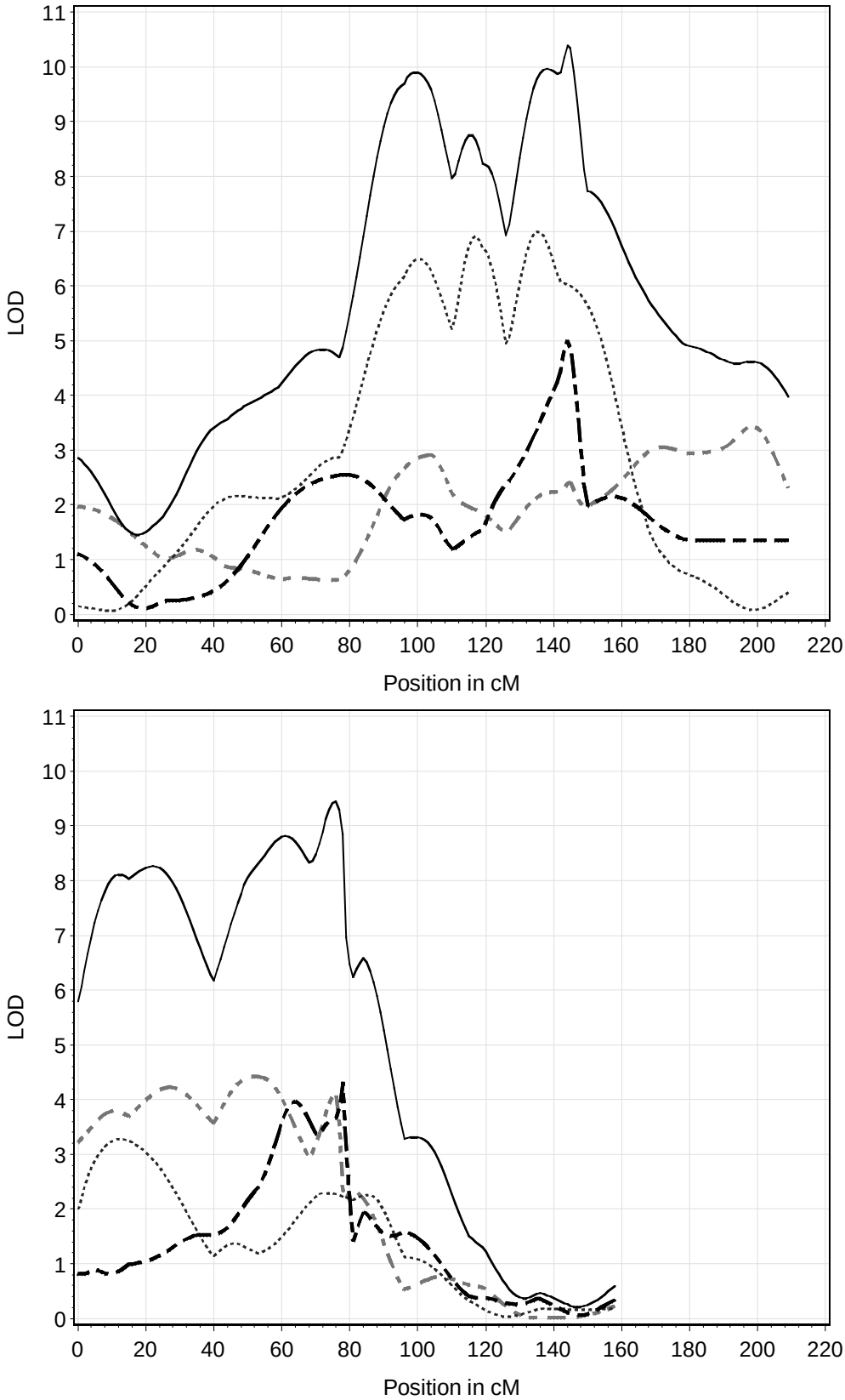

Figure 1: LOD-score profiles for back fat depth on chromosome 1 (top) and on chromosome 2 (bottom). The soild black line denotes the results from the joint analysis; the dashed gray (small dotted, black deshed) line denotes the results of the MxP (WxP, WxM) analysis; the genetic map is given in the additional files.

Discussion

QTL results

Because numerous QTL were mapped in the joint design, we will not discuss all identified QTL in detail. For a comparison of QTL found in this study and found by other groups see entries in the database pigQTLdb (Hu et al. [1]). Some QTL have also been reported by various other groups (e.g. QTL for carcass weight on SSC4). Other QTL are novel (e.g. QTL for back fat on SSC11 and SSC18). The signs of the breed effects are often, but not always, consistent with the history of the breed. For example, the Meishan breed is known to be a fatty breed, and it would subsequently be expected that most of the M breed allele effects at the QTL for back fat depth are higher compared to the P and W breed alleles. However, this was not always observed (Table 2). For daily gain and carcass weight traits, the breed allele effects of breed P are generally the highest (Tables 3 and 4), which fits to the breeding history of P. The P breed is frequently used as a sire line for meat production and daily gain and carcass weight are part of the breeding goal. Naturally, wild pigs have not been subject to artificial selection for the three traits; their breed allele effects were almost always lowest for the three traits (Tables 2 to 4). Because the P breed was selected for increase in daily gain and carcass length and M is a much heavier and fattier breed than W, this was expected for daily gain and carcass length. Additionally, because P was selected against back fat during the last decades and W is a lean breed, the breed effects of M and P are frequently the same and lower than the fatty M breed allele effect (Table 2).

Three QTL with imprinting effects were found on SSC7 of which two were paternally imprinted. The mode of imprinting was not clear for imprinted carcass weight QTL (Table 6), because nearly the same paternal and maternal additive effects were observed in the M breed. De Koning et al. [20] have mapped a maternal expressed QTL for muscle depth on the same chromosome. A well known gene causing an imprinting effect is *IGF2*, which is located in the proximal region of SSC2 (Nezer et al. [21], van Laere et al. [22]). De Koning et al. [20] have mapped an imprinted QTL for back fat thickness with paternal expression close to the *IGF2* region. In our study, we found an imprinted QTL in the corresponding chromosomal region for this trait as well (Tables 2 and 6), but it was not possible to unravel the mode of imprinting. A critical question is: are the detected imprinting effects really due to imprinting? As mentioned by Sandor and Georges [23] the number of imprinted genes in mammals has been estimated to be only around 100, which is not in a good agreement with the number of mapped imprinting QTL. The assumption underlying the classical model (4) for the detection

of imprinting is that the F_1-individuals are all heterozygous at the QTL. It has been shown by de Koning et al. [24] that in cases where this assumption is violated, the gene frequencies in the F_1-sires and F_1-dams may vary randomly, which might result in a significant, but erroneous, imprinting effect. This is especially a problem, when the number of males in the F_1-generation is low, as in this study. The assumptions of model (4) and the pitfalls regarding imprinting effects do also hold in model (3). The additive effects were estimated depending on their parental origin, and if the F_1-sires are not heterozygous at the QTL the estimates of the additive effects might differ depending on their parental origin, resulting in a significant imprinting effect. Hence, some cautions have to be made when drawing specific conclusions regarding the imprinting effects, especially for the imprinted QTL with an inconsistent mode of imprinting (Table 6). In some cases, imprinting effects might be spurious and due to within-founder breed segregation of QTL. Besides, the importance of imprinting for these traits has also been reported on a polygenic level within purebred pigs by Neugebauer et al. [25]. In addition, the same mode of imprinting in different founder alleles (Table 6) can be seen as evidence for real imprinting effects for these QTL.

Experimental design and methods

When QTL experiments are analysed jointly, several requirements have to be fulfilled. Ideally, identical or to a large extent identical markers have to be genotyped in the designs and the allele coding has to be standardised. Subsequently, a common genetic map has to be established. Trait definition and measurement have to be standardised and, ideally, housing and rearing conditions of the animals should be the same or similar. All these points were fulfilled in the present study, since to a large extent the same markers were used, all animals were housed and slaughtered at one central unit and phenotypes were recorded by the same technical staff. Furthermore, due to the connectedness of the three designs, the situation for a combined analysis is especially favourable and allowed the use of model (3). Compared to a separate analysis, fewer parameters are estimated (i.e. seven instead of nine). Additionally the number of meioses used simultaneously was roughly three times higher. This led to the high statistical power of the joint design, which is confirmed by the large number of mapped QTL and by the reduced width of the confidence intervals. The high experimental power is probably due to the fact that not only the same founder breeds were used, but also to some extent the same founder animals within breeds. Hence the same founder alleles could be observed in the individuals of two F_2-crosses, which increased the number of observations to

estimate the effects. This is especially the case for the WxM and WxP crosses, which both go back to one and same W boar.

Model (3) was adapted from Liu and Zeng [10] but was extended for imprinting effects. Modelling imprinting seemed to be important for these traits. Ignoring imprinting resulted in a reduced number of mapped QTL for all three traits. Besides, all purely mendelian QTL (i.e. non-significant imprinting) were also found when imprinting was modelled. Hence, estimating two additional parameters in order to model imprinting obviously did not reduce the power to map purely mendelian QTL, favouring the model with imprinting. Thereby it was important to account for heterogeneous residual variances. A substantial heterogeneity was expected given the variation of the phenotypes within and across the three crosses (Table 1) and could be due to the different number of QTL segregating in the three crosses. Following this, it could be assumed that the heterogeneity would be reduced if more QTL were added as cofactors in the model. In Figure 2, the plots of the residual variances are shown for the three crosses and different number of QTL included in the model. It can be seen that the residual variances decreased and the differences became smaller, but did not disappear. One reason for this could be that there are still many more QTL segregating, which were not detected because their effects are too small. Indeed, Bennewitz and Meuwissen [26] have used QTL results from a separate analysis of the same three crosses to derive the distribution of QTL effects. They have shown that the additive QTL effects are exponentially distributed with many QTL of small effects. Model (3) was also flexible with regard to the number of QTL alleles, which was important given the large number of QTL with three different breed allele effects (Tables 2 to 4).

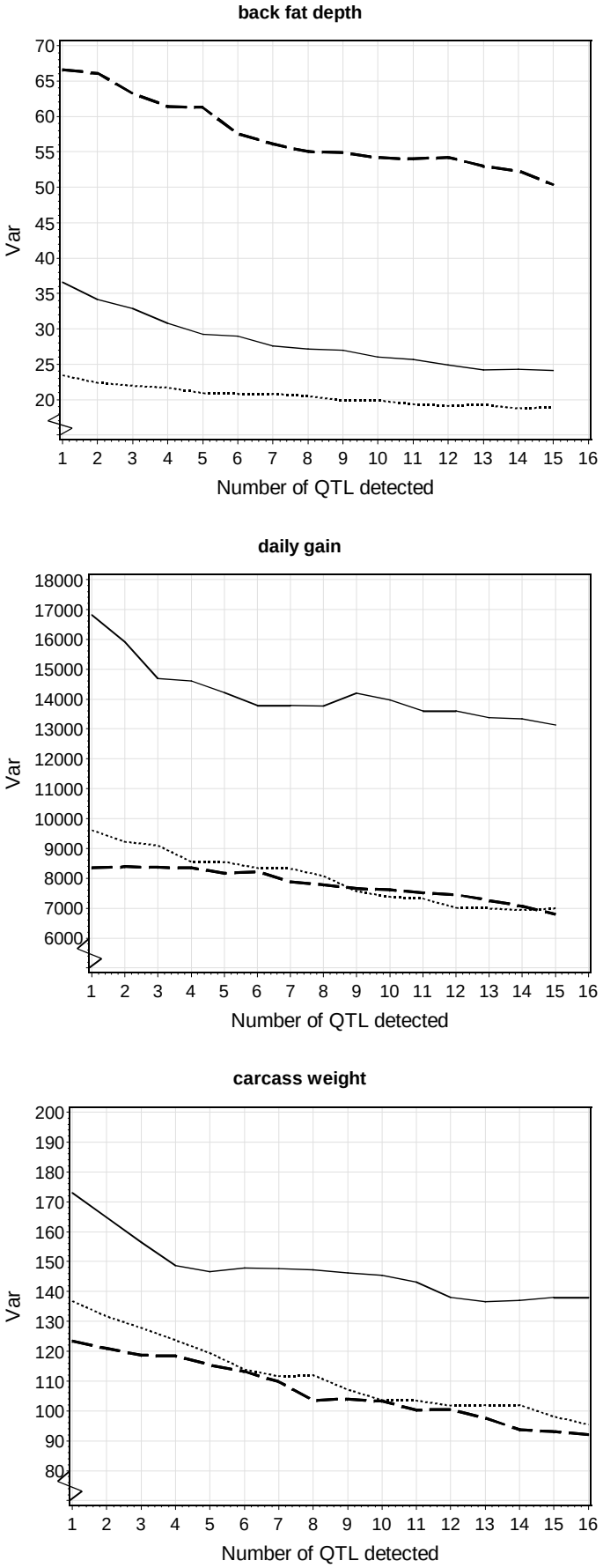

Figure 2: Residual variance plotted against the number of QTL included in the model. Solid line (dotted line, dashed line) denotes for the MxP cross (WxP cross, WxM cross).

Figure 2 also shows the benefit of including multiple QTL as cofactors in the model. The residual variances reduced continuously, which led to the increased statistical power and subsequently contributed to mapping the large number of QTL. The inclusion of QTL as cofactors is also known as composite interval mapping (CIM) and goes back to Zeng [27, 28] and Jansen and Stam [29]. There are basically two main reasons for applying CIM. The first is to decrease residual variance and increase statistical power, as also used in this study. The second is to unravel a chromosomal position harbouring a QTL more precisely, i.e. to separate multiple closely linked QTL. This also requires scanning the chromosomal region of QTL identified in previous rounds of cofactor selection (in our study also rescanning confidence intervals of identified QTL), which, however, requires dense markers in those regions. Because marker density was not very high in this study, no attempts were made to detect multiple QTL within a QTL confidence interval. Low marker density should also be kept in mind when interpreting multiple QTL on single chromosomes, because the amount of information to separate them is limited.

The high statistical power is also due to the defined relative low significance level (i.e. 5% chromosome-wise). Hence, correction for multiple testing was done only for chromosomes or chromosome-segments and not for the whole genome or even for the whole experiment considering all three traits. The low significance level was chosen because a large number of QTL with small effects are segregating in this design [26], and many QTL with small effects would not have been found using a more stringent significance level. The downside of this strategy is, of course, that some mapped QTL will be false positives. The applied methods were computationally fast, mainly because of the applied regression approach, but also because the quick method was used [15] for the significance threshold determination rather than applying the permutation test. Piepho [15] has shown that this method is a good approximation if the data are normally distributed, which was the case in this study (not shown). Alternatively, a permutation test could have been used, which would result in more accurate threshold values and, as proposed by Rowe et al. [30, 31], also for a more sophisticated identification of dominance and imprinting effects. This should be considered in putative follow-up studies.

Conclusions

The present study showed the strength of analysing three connected F_2-crosses jointly to map numerous QTL. The high statistical power of the experiment was due to the reduced number

of estimated parameters and to the large number of individuals. The applied model was flexible with regard to the number of QTL and QTL alleles, mode of QTL inheritance, and was computationally fast. It will be applied to other traits and needs to be expanded to account for epistasis.

Appendix

As stated in the main text, the restriction shown in eq (1) resulted in a re-parameterisation of the genetic model presented in eq (2). The re-parameterised model is as follows.

$$\begin{bmatrix} g_{MM}^{pm} \\ g_{PP}^{pm} \\ g_{WW}^{pm} \\ g_{MP}^{pm} \\ g_{PM}^{pm} \\ g_{MW}^{pm} \\ g_{WM}^{pm} \\ g_{WP}^{pm} \\ g_{PW}^{pm} \end{bmatrix} = \begin{bmatrix} 1 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & 0 & 0 & 0 \\ -1 & -1 & -1 & -1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 1 & 1 & 0 & 0 \\ 0 & 1 & 1 & 0 & 1 & 0 & 0 \\ 1 & -1 & 0 & -1 & 0 & 1 & 0 \\ -1 & 1 & -1 & 0 & 0 & 1 & 0 \\ -1 & 0 & -1 & 1 & 0 & 0 & 1 \\ 0 & -1 & 1 & -1 & 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} a_i^p \\ a_i^m \\ a_j^p \\ a_j^m \\ d_{MP} \\ d_{MW} \\ d_{PW} \end{bmatrix} + \begin{bmatrix} \mu \\ \mu \\ \mu \\ \mu \\ \mu \\ \mu \\ \mu \\ \mu \\ \mu \end{bmatrix}$$

The upper subscripts denote or the parental origin (i.e. either paternal (p) or maternal (m)) and the lower subscripts denote the breed origin M, P, and W. This model contained only four additive effects (two paternal and two maternal). Using the above notation, $a_M^P = a_i^P$, $a_P^P = a_j^P$, and $a_W^P = -(a_i^P + a_j^p)$. The same holds for the maternal alleles. The applied regression model (eq (3) in the main text) estimated the four additive effects for the breeds M and P. The two effects for W not modelled were reconstructed, as shown above.

Additional file 1:
Genetic map (marker name and distance from the start of the chromosome). The genetic map, including the marker names and the distance from the start of the chromosome

SSC1; SW1514 [0.0]; SWR485 [25.4], SWR2300 [43.5]; S0008 [59.3]; SW2130 [77.3]; EEF1A1 [95.8]; IGFR [104.1]; SW307 [110.3]; S0082 [119.2]; SW780 [126.3]; SW803 [141.7]; TPM2 [144.7]; TGFBR1 [149.6]; SW705 [178.5]; EAA [209.1]

SSC2; SW2443 [0.0]; SWC9 [5.2]; SW2623 [14.9]; S0141 [39.9]; SW240 [52.9]; MLP [68.0]; MYOD1 [70.6]; MEF2B [76.5]; UBL5 [77.8]; RETN [78.3]; INSR [78.3]; SW395 [81.0]; CDF [84.3]; S0010 [96.0]; S0378 [115.1]; FBN2 [119.4]; SW2192 [135.5]; S0036 [158.4]

SSC3; SERPINE1 [0.0]; SW72 [11.6]; S0206 [35.9]; ASPN [50.2]; OIF [50.8]; SW902 [57.9]; SW828 [74.0]; SW314 [104.6]; LPW [116.1]; SW [138.6]

SSC4; SW489 [0.0]; CMYC [19.7]; SW835 [27.7]; SWR73 [43.6]; SW2128 [50.9]; S0145 [50.9]; SW1073 [62.1]; SW1089 [67.3]; VATP [69.1]; ATP1B1 [71.6]; S0073 [75.3]; ATF6 [78.5]; OCT1 [79.1]; HSD17B7 [79.9]; SDHC [80.1]; MPZ [80.1]; APOA2 [80.2]; CASQ1 [81.0]; ATP1A2 [81.8]; MEF2D [82.5]; LMNA [84.6]; GBA [85.1]; PKLR [85.6]; IVL [87.6]; EAL [93.7]; ATP1A1 [95.8]; TSHB [98.1]; NGFB [99.6]; AMPD1 [100.2]; SW2435 [107.7]; AGL [121.5]; S0097 [135.9]; PXMP1 [142.8]; CNN3 [142.8]

SSC5; SW413 [0.0]; SWR453 [39.0]; SW2425 [53.0]; SW2 [64.4]; S0005 [77.3]; SW152 [92.2]; IGF1 [110.0]; SW995 [120.1]; DCN [131.5]; MYF5_DDEI [150.4]; SW967 [157.9]

SSC6; S0035 [0.0]; SW1329 [24.8]; SW1057 [58.1]; FTO [73.7]; S0087 [80.0]; ETH5001 [94.4]; RYR [96.4]; LIPE [98.3]; TGFB1 [99.5]; A1BG [101.2]; EAH [102.4]; SKI [106.0]; BNP1 [112.0]; HFABP [124.9]; ID3 [127.1]; S0146 [141.5]; S0003 [150.4]; SW824 [165.7]; LERP [177.9]; P3 [207.8]; EAO [235.5]

SSC7; S0025 [0.0]; S0064 [36.3]; SWR1078 [50.0]; ID4_ECO [61.3]; ID4_SMA [61.3]; CYPD [73.3]; CYPA [73.3]; KE6 [75.2]; TNFA [75.5]; TNFB [76.2]; S0102 [86.5]; PSMA4 [100.9]; PLIN [106.8]; S0066 [113.0]; S0115 [143.3]; FOS [149.7]; SW581 [173.9]; S0212 [196.7]; AACT2 [206.0]; PO1A [206.2]; PI2 [208.8]; IGH2 [229.5]

SSC8; SW905 [0.0]; PGCMUT [18.0]; SW933 [34.0]; SW1070 [49.4]; S0144 [85.0]; SW16 [110.1]; SW61 [127.1]; OPN [151.8]

SSC9; EAK [0.0]; HPX [19.8]; SW21 [28.7]; SW911 [59.1]; SLN [71.0]; SW2074 [80.0]; APOA1 [89.5]; LPR [110.1]; EAN [113.0]; PDK4 [113.8]; PDK4i [113.8]; PDK41 [113.8]; IL6 [117.1]; VISF [125.6]; VISF_PRO [125.6]; PRKAR2B [127.3]; PIC3CG [127.3]; MYOG [130.9]; SW1435 [132.5]; SW2093 [135.6]; GLUL [147.5]; SW174 [158.1]; S0114 [161.3]; EAE [187.4]; SW1349 [194.6]

SSC10; SW830 [0.0]; SW443 [30.6]; SW497 [52.5]; GAS1 [74.1]; SWR1849 [82.7]; SW2000 [105.7]; SW1708 [125.0]; SW2067 [150.8]

SSC11; S0392 [0.0]; POSTN [22.6]; SW1632 [28.4]; SW435 [61.0]; SW1827 [93.3]

SSC12; S0143 [0.0]; EAD [10.8]; SW957 [32.0]; GH1-H [40.7]; GH1-A ; S0083 [51.0]; SW874 [64.5]; S0090 [84.1]; S0147 [99.3]; S0106 [109.8]; SWR1021 [127.1]; SW605 [137.9]

SSC13; S0282 [0.0]; S0076 [39.2]; SW864 [60.8]; SWR1008 [70.7]; TF [81.2]; S0068 [94.2]; POU1F1 [108.2]; SW520 [120.5]; SW38 [152.6]; S0215 [179.0]; CSTB [204.4]

SSC14; EDG3 [0.0]; SW857 [27.5]; SW2038 [43.8]; SW540 [60.7]; ACTN2 [70.6]; ACTA1 [78.0]; SW210 [84.3]; SW2488 [105.1]; SW55 [122.1]; SW2515 [151.2]

SSC15; KS169 [0.0]; S0148 [21.2]; EAG [31.3]; SW964 [41.9]; SW15 [52.5]; SW2053 [71.9]; SW1983 [99.4]

SSC16; S0111 [0.0]; SW1035 [21.2]; SW419 [33.3]; S0077 [43.9]; S0026 [61.5]; SWR2480 [69.4]; SPARC [78.4]; S0061 [98.0]

SSC17; SW335 [0.0]; SW1891 [6.5]; S0296 [15.6]; SW1920 [41.3]; GHRH [43.6]; RNPC2 [45.4]; SJ063 [69.9]; GNAS [86.4]; EEF1A2 [94.6]; SW2427 [97.9]

SSC18; SW1808 [0.0]; EAI [10.9]; LEPTIN [33.5]; SW787 [43.6]; S0062 [58.8]; GCK [71.2]

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

CR did the statistical analysis and JB developed the models. Both authors drafted the manuscript.

Acknowledgements

CR received funding from the H. Wilhelm Schaumann Stiftung, Hamburg, Germany. Both authors thank H.-P. Piepho from the University of Hohenheim for helpful discussions and carefully reading of the manuscript, N. Reinsch from the Research Institute of Farm Animal Biology in Dummerstorf, Germany, for the use of his Fortran program Bigmap, and C. Baes for language corrections. The manuscript has benefited from the critical and very helpful comments of two anonymous reviewers and of the editor.

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CHAPTER TWO

Mapping QTL for metabolic and cytological fatness traits of connected F_2-crosses in pigs

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Published in:

Journal of Animal Science **(2012), 90(2),pp. 399-409**

ISSN: 00218812

doi: 10.2527/jas.2011-4231

Mapping QTL for metabolic and cytological fatness traits of connected F_2-crosses in pigs

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Abstract

In the present study three connected F_2 crosses were used to map QTL for classical fat traits as well as fat related metabolic and cytological traits in pigs. The founder breeds were Chinese Meishan, European Wild Boar and Pietrain with to some extent same founder animals in different crosses. The different selection history of the breeds for fatness traits as well as the connectedness of the crosses led to a high statistical power. The total number of F_2 animals varied between 694 and 966, depending on the trait. The animals were genotyped for around 250 genetic markers, mostly microsatellites. The statistical model was a multi allele multi QTL model that accounted for imprinting. The model was previously introduced from plant breeding experiments. The traits investigated were back fat depth and fat area as well as relative number of fat cells with different sizes and two metabolic traits, i.e. soluble protein content as an indicator for the level of metabolic turnover and NADP-malat dehydrogenase as an indicator for enzyme activity. The results revealed in total 37 significant QTL on chromosomes 1, 2, 4, 5, 6, 7, 8, 9, 14, 17 and 18, with often an overlap of confidence intervals of several traits. These confidence intervals were in some cases remarkably small, which is due to the high statistical power of the design. In total 18 QTL showed significant imprinting effects. The small and overlapping confidence intervals for the classical fatness traits as well as for the cytological and metabolic traits enabled positional and functional candidate gene identification for several mapped QTL.

Key Words

candidate genes, fatness traits, imprinting, pig, quantitative trait loci

Introduction

Fat related traits are frequently included as a goal of pig breeding programmes. Many QTL mapping experiments have been conducted to find loci affecting fat traits and numerous QTL have been reported (Hu et al., 2005). Most studies used fat traits defined in a rather classical way, e.g. back fat thickness or intramuscular fat. These traits can be seen as end products within a cascade of physiological steps, which are controlled by gene products like enzymes. For the interpretation of QTL results and the identification of genes and pathways underlying the QTL it might be advantageous to have some trait measurements of the direct gene products. Specifically, body fat tissue results from development of adipocytes and deposition of fat into these cells, with the latter mainly influenced by lipogenesis and lipolysis. It was shown that the adipocytes of pigs with a higher propensity to fatten had a

higher volume of fat cells (Etherton, 1980; Scott et al., 1981). Lipogenic enzyme activities have also been associated with different level of fat deposition in pigs (Hood and Allen, 1973). Following this, it would be desirable to have trait measurements of adipocyte characteristics as well as specific enzyme activities regulating lipogenesis in order to better understand mapped fat trait QTL.

The advantage of using metabolic and cytological traits was demonstrated by Demars et al. (2007) who were able to better characterise the underlying nature of a QTL for body fatness mapped on SSC7 than using solely classical fatness traits. Geldermann et al. (2010) considered numerous classical fat traits as well as measurements of fat related enzyme activity and number and volume of fat cells. They analysed three porcine F_2 crosses that are connected by same founder breeds and animals. The founder breeds were Chinese Meishan, European Wild Boar and Pietrain. For analysing fat traits, these founder breeds are especially well suited because it is known that they differ markedly in the level of fat deposition (e.g. Mourot et al., 1996), with Meishan being a fatty and Pietrain a lean breed. The statistical model applied by Geldermann et al. (2010) was simple and they treated each cross separately although they are connected. Additionally, they ignored putative parent of origin effects, which are, however, frequently reported for fat traits in pigs.

The aim of this study was to conduct a joint QTL study of the three connected F_2 crosses described by Geldermann et al. (2010) using selected metabolic, enzymatic and cytological fat traits. For this purpose, the multi QTL multi allele model of Rückert and Bennewitz (2010) was used, which also modelled imprinting effects. This model is tailored to analyse connected F_2 crosses jointly, leading to a higher statistical power to detect QTL. Based on QTL results across traits, positional and functional candidate genes are suggested.

Materials and methods

Animals and traits

The experimental design was described in detail by Geldermann et al. (2010). Briefly, the first cross (MxP) was obtained by mating one Meishan (M) boar with eight Pietrain (P) sows. The second cross (WxP) was generated by mating one European Wild Boar (W) boar with nine P sows and the third cross (WxM) was obtained by mating the same W boar with four Meishan (M) sows. The number of F_2 individuals in the MxP (WxP, WxM) was 316 (315, 335), but varied for some traits, see Table 1.

Table 1: Description of the traits with abbreviations (Abbr.) and summary statistics within and across the three crosses, number of observations (n), mean, standard deviation (Sd), minimum (Min) and maximum (Max) of the phenotypic observations.

Trait	Abbr.	Cross	n	Mean	Sd	Min	Max
Average back fat depth (mm)	BFD	MxP	316	27.93	6.68	8.70	46.00
		WxP	315	22.82	4.98	10.30	40.00
		WxM	335	31.82	6.68	8.30	48.70
		Joint	966	27.61	7.19	8.30	48.70
Fat area (cm*cm)	FA	MxP	316	20.85	5.89	5.52	38.80
		WxP	313	16.71	5.52	4.24	37.45
		WxM	335	24.42	6.59	4.18	47.44
		Joint	964	20.75	6.80	4.18	47.44
Soluble protein content (mg/g tissue)	SPC	MxP	315	3.59	1.54	0.63	12.97
		WxP	315	4.86	1.73	2.30	13.30
		WxM	326	3.49	1.12	1.47	8.79
		Joint	956	3.98	1.60	0.63	13.30
NADP-malat dehydrogenase (units/g tissue)	MDH	MxP	315	0.61	0.27	0.07	2.18
		WxP	315	0.45	0.18	0.11	1.22
		WxM	326	0.51	0.19	0.14	1.33
		Joint	956	0.52	0.23	0.07	2.18
Relative number of fat cells with medium cell sizes, 73-146 µm (%)	FCL	MxP	307	46.37	19.02	5.11	79.48
		WxP	296	56.41	14.80	7.06	82.99
		WxM	91	30.99	17.99	1.90	76.41
		Joint	694	48.63	19.08	1.90	82.99
Relative number of fat cells with large cell sizes, >146 µm (%)	FCH	MxP	307	16.86	13.93	0.37	63.21
		WxP	296	5.57	5.78	0.36	39.48
		WxM	91	16.16	12.51	0.41	50.25
		Joint	694	11.85	12.27	0.36	63.21

Back fat tissue was collected between the skin and *musculus longissimus dorsi* at the $13^{th}/14^{th}$ rib at slaughter. After some preparation, enzyme activity and the soluble protein content were measured in the fat tissues. Additionally, fat cells were extracted from fat tissue and the diameter of each cell was determined. See Geldermann et al. (2010) for details regarding the used protocols. The traits back fat depth (BFD), measured as an average of measurements at the 10^{th} rib, shoulder and loin, and the back fat area (FA) at $13^{th}/14^{th}$ rib were considered representative of classical back fat performance traits in this study. The total soluble protein content (SPC) and the NADP-malate dehydrogenase (MDH) activity were used as indicators for metabolic and enzyme activities, respectively. The two cytological traits relative number of fat cells with medium cell size (FCL, calculated as the proportion of fat cells with a diameter between 73 and 146 µm) and large cell size (FCH, calculated as the proportion of cells with a cell size larger than 146 µm) were used. For summary statistics

within and across the three crosses see Table 1. The phenotypes were pre-corrected for the effect of sex, litter, season and slaughter age before QTL analysis.

Statistical analysis

The animals were genotyped genomewide for around 250 markers, mainly microsatellites, but also SNPs. A genetic map was calculated across the three crosses as described in detail by Rückert and Bennewitz (2010). Because many markers were genotyped in all three or in at least two crosses, the estimation of a common map was straightforward. The map can be found in Rückert and Bennewitz (2010) and is in agreement with other published maps. The QTL analysis was done using the model of Rückert and Bennewitz (2010) which was adapted from plant breeding experiments and is tailored to analyse connected multiple experimental crosses. The model assumed that two founder breeds of a certain cross are divergent homozygous at a certain QTL. For each F_2 individual of a certain cross four genotype probabilities $pr(Q_i^p Q_i^m)$, $pr(Q_j^p Q_i^m)$, $pr(Q_i^p Q_j^m)$ and $pr(Q_j^p Q_j^m)$ were calculated for each chromosomal position. The upper subscripts denotes the parental origin of the alleles (i.e. paternal (*p*) or maternal (*m*) derived) and the lower subscript denotes the breed origin of the alleles (i.e. breed *i* or *j*, with *i*, *j* being breed M, P, or W, respectively). From these genotype probabilities the probability of an F_2 individual *k* from a certain cross, say WxM receiving a QTL allele from one founder breed, say M, from its father was calculated as $z_{M,k}^p = pr(Q_M^p Q_M^m) + pr(Q_M^p Q_W^m)$. Similarly, the probability of receiving the founder breed allele M from its mother was calculated as $z_{M,k}^m = pr(Q_M^p Q_M^m) + pr(Q_W^p Q_M^m)$. The calculation for the founder breed allele W was done in the same manner. These probabilities were also calculated for the offspring of the other two crosses MxP and WxP. The probability of an F_2 individual being heterozygous was calculated as the sum of the two heterozygous genotype probabilities, i.e. $z_{ijk} = pr(Q_i^p Q_j^m) + pr(Q_j^p Q_i^m)$. These probabilities can be used to establish a regression model. However, because the sum of the additive effects within each parental origin is equal to zero, such a model would be overparametrised (see Rückert and Bennewitz, 2010). Therefore, a reparametrisation was done as $\tilde{z}_{M,k}^p = z_{M,k}^p - z_{W,k}^p$, $\tilde{z}_{P,k}^p = z_{P,k}^p - z_{W,k}^p$, $\tilde{z}_{M,k}^m = z_{M,k}^m - z_{W,k}^m$, and $\tilde{z}_{P,k}^m = z_{P,k}^m - z_{W,k}^m$. Thus, the final regression model was

$$y_{ijk} = cross_{ij} + a_M^p \tilde{z}_{M,k}^p + a_M^m \tilde{z}_{M,k}^m + a_P^p \tilde{z}_{P,k}^p + a_P^m \tilde{z}_{P,k}^m + d_{MW} z_{MW,k} + d_{MP} z_{MP,k} + d_{WP} z_{WP,k} + e_{ijk}$$

The term $cross_{ij}$ denotes the fixed effect of the F_2 cross. The residual variance was assumed to be heterogeneous, i.e. $e_{ijk} \sim N(0, \sigma_{ij}^2)$. The model produced estimates of the additive breed effects of breeds M and P considering the parental origin of the alleles ($\hat{a}_M^p, \hat{a}_M^m, a_P^p, \hat{a}_P^m$). The additive effects of the W breeds were estimated as $\hat{a}_W^p = -(\hat{a}_M^p + \hat{a}_P^p)$ and $\hat{a}_W^m = -(\hat{a}_M^m + \hat{a}_P^m)$. Combined mendelian additive effects (i.e. ignoring parental origin of the alleles) were calculated as $\hat{a}_M = \hat{a}_M^p + \hat{a}_M^m$, $\hat{a}_P = \hat{a}_P^p + \hat{a}_P^m$, and $\hat{a}_W = -(\hat{a}_M^p + \hat{a}_M^m + \hat{a}_P^p + \hat{a}_P^m)$. The three *d* terms represent the dominant QTL effects. The model was fitted every cM on the autosomes by adapting the *z* terms accordingly. The test statistic was an *F*-test; the *F*-values were converted into LOD-scores as $LOD \approx (np * F)/(2 * \log(10))$, with *np* being the number of estimated QTL effects, i.e. *np* = 7 (four additive and three dominance effects). The global null hypothesis was that at the chromosomal position with the highest test statistic every estimated parameter is equal to zero. The 5% threshold of the test statistic corrected for multiple testing on the chromosome was obtained using the quick method of Piepho (2001). This low significance level was chosen because a large number of QTL with small effects are segregating in this design (Benenwitz and Meuwissen 2010). Once the global null hypothesis was rejected, the following subhypotheses were tested at significant chromosomal positions by building linear contrasts.

Test for an additive QTL:

$H_0: a_M^p + a_M^m = 0$ and $a_P^p + a_P^m = 0$, $H_1: a_M^p + a_M^m \neq 0$ and / or $a_P^p + a_P^m \neq 0$.

Test for dominance at the QTL:

$H_0: d_{MW} = d_{MP} = d_{WP} = 0$, H_1: at least one different from zero.

Test for imprinting at the QTL:

$H_0: a_M^p = a_M^m$ and $a_P^p = a_P^m$, $H_1: a_M^p \neq a_M^m$ and / or $a_P^p \neq a_P^m$.

The test of the three subhypotheses resulted in the three error probabilities p_{add}, p_{dom}, and p_{imp} for additive, dominance and imprinting QTL, respectively. Additionally, it was assessed how many QTL alleles could be distinguished based on their additive effects. This was done by testing the segregation of the QTL in each of the three crosses, considering only additive mendelian effects (i.e. ignoring imprinting and dominance). For each significant QTL a confidence interval was calculated using the one LOD drop method. Multiple QTL were included as cofactors in the model using a forward selection approach. For details see Rückert and Bennewitz (2010).

Results

The summary statistics (Table 1) showed that there is substantial variation within and across the three crosses. For BFD and FA the highest and lowest mean was in the WxM and WxP cross, respectively. The highest and lowest mean for soluble protein content was observed for WxP and WxM, respectively.

The QTL results are presented in Tables 2, 3 and 4. In general, numerous QTL were reported, most of them on SSC 1, 2, 6, 7, 17, and 18. Several QTL showed significant imprinting effects, especially on SSC 2 and 6. In many cases three QTL alleles could be distinguished. The confidence intervals were sometimes remarkably small, given that only linkage information is used.

Table 2: QTL results for average back fat depth (BFD) and fat area (FA) with confidence intervals (CI), test statistics, error probabilities and order of estimated breed QTL effects

Trait	SSC	Pos	CI [a]		*F*-value	p_{add} [b]	p_{dom} [c]	p_{imp} [d]	Mode[e]	Order of effects[f]
BFD	1	131	[SW307; [110.3;	SW803] 141.7]	5.52	<0.001	0.801	0.905	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	2	9	[SW2443; [0.0;	S0141] 39.9]	4.21	0.014	1.000	<0.001	(mat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	2	76	[S0141; [39.9;	SW395] 81.0]	5.03	<0.001	0.183	0.404	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	6	100	[RYR; [96.4;	A1BG] 101.2]	7.07	<0.001	0.001	0.002	(pat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	7	75	[ID4SMA; [61.3;	TNFB] 76.2]	8.02	<0.001	0.172	0.076	(- -)	$\hat{a}_P > \hat{a}_W > \hat{a}_M$
	9	194	[EAE; [187.4;	SW1349] 194.6]	3.59	0.019	0.002	0.290	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
FA	1	145	[SW803; [141.7;	TGFBR1] 149.6]	6.52	<0.001	0.097	0.033	(nc)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	2	25	[SWC9; [5.2;	S0141] 39.9]	4.85	0.014	0.702	<0.001	(nc)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	2	77	[MYOD1; [70.6;	SW395] 81.0]	3.66	0.001	0.087	0.315	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	6	100	[RYR; [96.4;	A1BG] 101.2]	5.04	<0.001	0.125	0.014	(pat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	7	87	[CYPA; [73.3;	PLIN] 106.8]	3.31	0.002	0.152	0.082	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	14	53	[SW2038; [43.8;	SW540] 60.7]	3.11	0.002	0.024	0.320	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	17	92	[SJ063; [69.9;	SW2427] 97.7]	2.86	0.061	0.484	0.004	(nc)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	18	29	[EAI; [10.9;	SW787] 43.6]	2.79	0.003	0.102	0.457	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$

[a] confidence interval (CI); [b] error probability for additive effects; [c] error probability for dominant effects; [d] error probability for imprinting effects; [e] Mode of imprinting ((--) imprinting not significant, (mat) maternal imprinting, (pat) paternal imprinting, (nc) not consistent)), [f] $\hat{a}_P$ estimated effect of Pietrain breed, $\hat{a}_M$ estimated effect of Meishan breed, $\hat{a}_W$ estimated effect of wild boar breed

Table 3: QTL results for soluble protein content (SPC) and NADP malat dehydrogenase (MDH) with confidence intervals (CI), test statistics, error probabilities and order of estimated breed QTL effects

Trait	SSC	Pos	CI [a]	*F*-value	p_{add} [b]	p_{dom} [c]	p_{imp} [d]	Mode[e]	Order of effects[f]
SPC	2	22	[SWC9; S0141] [5.2; 39.9]	3.56	0.016	0.825	0.001	(mat)	$\hat{a}_P = \hat{a}_W > \hat{a}_M$
	3	96	[SW828; SW349] [74.0; 138.6]	3.24	0.001	0.842	0.050	(mat)	$\hat{a}_P = \hat{a}_W > \hat{a}_M$
	7	73	[ID4SMA; S0102] [61.3; 86.5]	3.39	<0.001	0.665	0.418	(- -)	$\hat{a}_P = \hat{a}_W > \hat{a}_M$
	14	105	[SW210; SW55] [84.3; 122.1]	2.69	0.001	0.295	0.923	(- -)	$\hat{a}_W > \hat{a}_M = \hat{a}_P$
	17	87	[SJ063; SW427] [69.9; 97.9]	3.69	0.003	0.035	0.039	(nc)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	18	33	[EAI; S0062] [10.9; 58.8]	3.98	0.015	0.003	0.030	(mat)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
MDH	2	15	[SWC9; S0141] [5.2; 39.9]	3.80	0.658	0.159	<0.001	(mat)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	7	69	[ID4SMA; S0102] [61.3; 86.5]	6.71	<0.001	0.831	0.151	(- -)	$\hat{a}_P > \hat{a}_W > \hat{a}_M$
	7	225	[PI2; IGH2] [208.8; 229.5]	3.19	0.659	0.001	0.152	(- -)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$

[a] confidence interval (CI); [b] error probability for additive effects; [c] error probability for dominant effects; [d] error probability for imprinting effects; [e] Mode of imprinting ((--) imprinting not significant, (mat) maternal imprinting, (pat) paternal imprinting, (nc) not consistent)), [f] $\hat{a}_P$ estimated effect of Pietrain breed, $\hat{a}_M$ estimated effect of Meishan breed, $\hat{a}_W$ estimated effect of wild boar breed

Table 4: QTL results for relative number of medium sized fat cells (FCL) and of high sized fat cells (FCH) with confidence intervals (CI), test statistics, error probabilities and order of estimated breed QTL effects.

Trait	SSC	Pos	CI [a]		*F*-value	p_{add} [b]	p_{dom} [c]	p_{imp} [d]	Mode[e]	Order of effects[f]
FCL	1	176	[TGFBR1; [149.6;	EAA] 209.1]	3.82	0.001	0.053	0.254	(- -)	$\hat{a}_P = \hat{a}_W > \hat{a}_M$
	4	98	[EAL; [93.7;	AGL] 121.5]	3.20	0.109	0.007	0.035	(mat)	$\hat{a}_P = \hat{a}_W > \hat{a}_M$
	5	110	[SW152; [92.2;	DCN] 120.1]	3.12	0.009	0.828	0.003	(pat)	$\hat{a}_P = \hat{a}_W > \hat{a}_M$
	6	25	[S0035; [0.0;	SW1057] 58.1]	3.27	0.002	0.397	0.056	(- -)	$\hat{a}_W > \hat{a}_M = \hat{a}_P$
	7	75	[ID4SMA; [61.3;	S0102] 86.5]	2.37	0.001	0.687	0.644	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	7	128	[S0066; [113.0;	S0115] 143.3]	5.79	0.001	0.001	0.023	(nc)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	8	116	[S0144; [85.0;	SW61] 127.1]	4.14	0.192	<0.001	0.306	(- -)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	17	46	[GHRH; [43.6;	SJ063] 69.9]	2.57	0.027	0.606	0.021	(pat)	$\hat{a}_W > \hat{a}_M = \hat{a}_P$
	18	37	[SW1808; [0.0;	SW787 43.6]	2.36	0.326	0.005	0.557	(- -)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
FCH	1	118	[SW307; [110.3;	SW780] 126.3]	3.65	0.001	0.070	0.021	(nc)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	2	14	[SW2443; [0.0;	S0141] 39.9]	5.32	0.004	0.386	<0.001	(mat)	$\hat{a}_M = \hat{a}_W > \hat{a}_P$
	6	99	[ETH5001; [94.4;	HFABP] 124.9]	5.13	0.016	0.001	0.013	(pat)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	7	75	[ID4SMA; [61.3;	S0102] 86.5]	4.68	<0.001	0.007	0.433	(- -)	$\hat{a}_P = \hat{a}_W > \hat{a}_M$
	14	53	[SW2038; [43.8;	SW540] 60.7]	2.91	0.022	0.016	0.260	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$

[a] confidence interval (CI); [b] error probability for additive effects; [c] error probability for dominant effects; [d] error probability for imprinting effects; [e] Mode of imprinting ((--) imprinting not significant, (mat) maternal imprinting, (pat) paternal imprinting, (nc) not consistent)), [f] $\hat{a}_P$ estimated effect of Pietrain breed, $\hat{a}_M$ estimated effect of Meishan breed, $\hat{a}_W$ estimated effect of wild boar breed

For BFD and FA (Table 2) QTL were found on SSC 1, 2, 6, 7, 9, 14, 17, and 18. All QTL showed a significant additive effect and the QTL on SSC 2, 6, and 17 also showed highly significant imprinting effects. The order of breed QTL effects is often (but not always; see QTL for BFD on SSC7, Table 2) M over P over W. For MDH and SPC, QTL results are shown in Table 3. For SPC ,QTL were found on SSC 2, 3, 7, 14, 17, and 18, with an overlap of confidence intervals with the QTL for the fat performance traits reported in Table 2. For the QTL on SSC 2, 17, and 18 imprinting was also significant. For MDH three QTL were found, two on SSC 7. Interestingly, the QTL on SSC 2 was only significant due to its imprinting effect and on SSC 7 due to its dominance effects. The breed QTL effect was typically P over W over M, if the additive effect was significant. For FCL, 8 QTL were found

(Table 4). Only two alleles could be distinguished for each QTL, the breed QTL effects of P and W were often similar. The QTL on SSC 2 reported for the other traits was not significant. For FCH, 5 QTL were found (Table 4). In contrast to FCL, each QTL for FCH showed an overlap of confidence intervals with the performance QTL listed in Table 2.

Discussion

This study analysed back fat traits and selected metabolic, enzymatic and cytological traits in the design described by Geldermann et al. (2010) using the multi QTL multi allelic model of Rückert and Bennewitz (2010). It analysed the connected crosses jointly and considered additive, dominant and also imprinting effects. This led to the elevated power of this approach compared to the approach used by Geldermann et al. (2010). Numerous QTL have been mapped with remarkably short confidence intervals. These intervals showed often an overlap across the traits, which can also be seen when comparing the plots of the test statistic against the chromosomal position for those chromosomes with QTL for several traits (Figure 1 and 2). This enabled a joint interpretation of the results. The discussion is organised as follows. In the next section general breed and imprinting effects are discussed. Thereafter QTL results of single chromosomes are discussed across traits and positional and functional candidate genes underlying the QTL are suggested. The paper ends with a short conclusion.

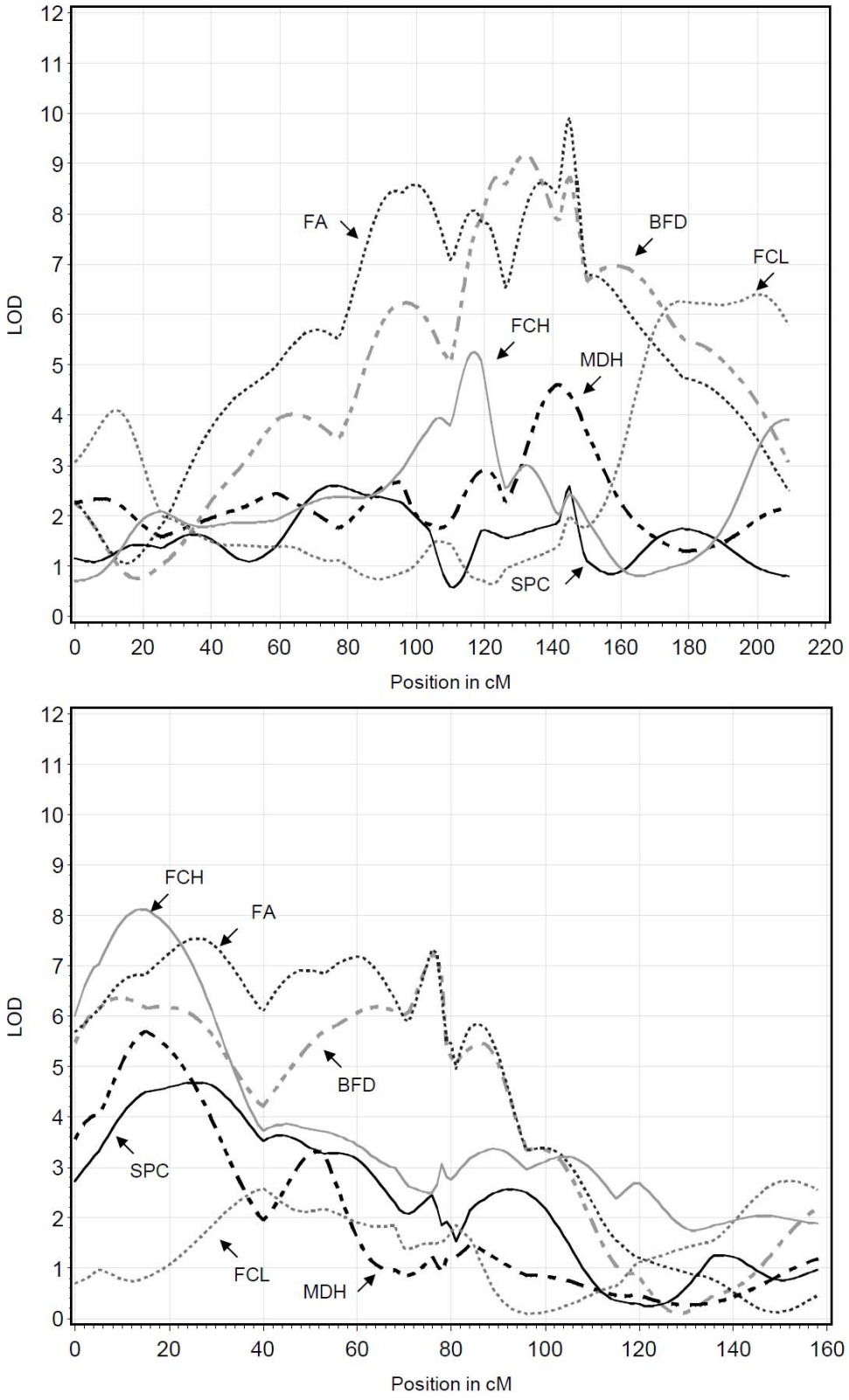

Figure 1: Plot of QTL test statistic for SSC1 (top) and SSC2 (bottom). For trait abbreviation see Table 1.

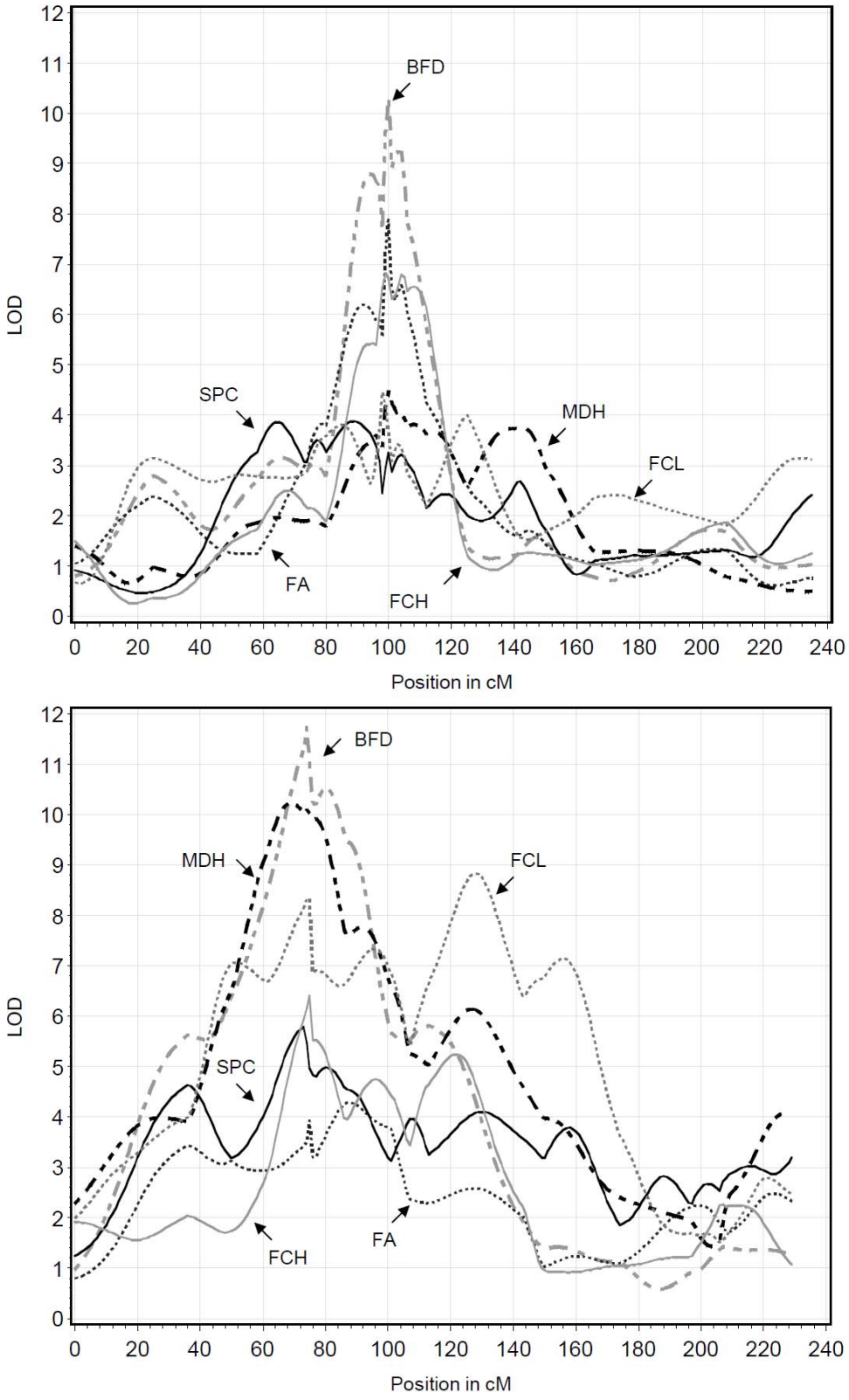

Figure 2: Plot of QTL test statistic for SSC6 (top) and SSC7 (bottom). For trait abbreviation see Table 1.

General breed and imprinting effects

The Meishan breed is known for its high propensity to accumulate back fat. The higher M breed allelic effects for the back fat traits (Table 2) were therefore expected. On the contrary, Pietrain has been selected for growth and meat content and less fat. This is also documented in the differences in the cross mean of these traits (Table 1). The mean of the MxP cross was in between the mean of the WxM and WxP cross. The trait soluble protein content accumulates the effect of non-specific enzyme activities and the higher number of mapped QTL was expected (Table 3). High soluble protein content is attributable to an elevated metabolic turn over. Following this, the higher cross mean of protein content in WxP and lower in WxM (Table 1) is a consequence of selection direction within these breeds. The allelic breed effects (Table 3) also pointed in this direction. This clear pattern of breed allelic effects and cross means was not observable for the remaining traits, which may also be due to limited statistical power to unravel small, but true differences.

A substantial proportion of QTL showed significant imprinting effects. However, as discussed in Rückert and Bennewitz (2010) some cautions have to be made when interpreting the statistical significant imprinting effects, as these might not always reflect true imprinting but are a result from within founder breed segregation. Especially if the mode of imprinting is not consisted across the breeds this can be seen as evidence against real imprinting effects, because it is unlikely that real imprinting differs across breeds. However, some imprinted QTL are within well known porcine imprinting regions, e.g. on SSC2 (Nezer et al., 1999; van Laere et al., 2003).

QTL results and candidate genes on SSC2

The proximal region of SSC2 contains the *IGF2* locus. The gene is imprinted and only paternally inherited alleles are expressed (e.g. de Koning et al., 2000; Boysen et al., 2011). The QTL found in our study on SSC2 within this chromosomal region (Tables 2 to 4) are in good agreement with this.

The second QTL on SSC2 for BFD and FA matches to the chromosomal position of the gene *InsR* (insulin receptor), which is a glycoprotein. It belongs to the receptor tyrosine kinases. The receptor is located in the membrane (Gu et al., 1992). Binding of insulin to its receptor is leading to a stimulation of lipogenese and inhibition of the lipolyse. Blüher et al. (2002) investigated the physiological role of insulin in adipose tissue by creating fat-specific insulin receptor knock out mice and found that knock out mice had markedly reduced fat mass, and exhibited heterogeneity in fat cell size. Hence, *InsR* plays an important role in the

pathway from insulin to fatty acid in adiposities and is also a functional candidate gene for this QTL, which should be considered in further functional studies.

QTL results and candidate genes on SSC5

Many studies mapped QTL for fat related traits on SSC5 (Bidanel et al., 2001; de Koning et al., 2001; Malek et al., 2001 a, b; Nii et al., 2006; Ramos et al., 2009; Tomas et al., 2010). In contrast to this, no QTL for BFD or FA was found in our study, but an imprinted QTL for FCL (Table 4). The chromosomal position is close to the insulin like growth factor 1 (*IGF1*). *IGF1* has been detected as a candidate gene in pigs (Roehe et al., 2003) and is involved in the regulation of growth and differentiation of different cell types, e.g. the replication and differentiation of pre-adiposities, and in the control of body weight (Kopecny et al., 2002). Additionally, Estany et al. (2007) investigated a polymorphic $(CA)_n$ sequence repeat, located at the first intron of *IGF1* in a Landrace and a Duroc population. The authors found a significant association between the length of the polymorphism and circulating *IGF1* level at 160 days. Furthermore, a negative correlation between intramuscular fat content and *IGF1* concentration at an age of 185 days was found. Rajkumar et al. (1999) investigated the role of *IGF1* in the accumulation of fat tissue in transgenic mice. They partially inhibited *IGF1* action by over expression of *IGFBP1* which binds *IGF1* and limits its bioavailability. The authors could demonstrate that transgenic mice, which overexpress *IGFBP1*, had a reduced epidermal fat mass and adipocyte size compared to wild-type mice. To confirm *IGF1* as a candidate gene underlying this QTL for FCL, the level of this gene expression in Pietrain should be compared to Meishan.

QTL results and candidate genes on SSC6

Paternally imprinted QTL were found on SSC6 in the distal region for both fat performance traits and for FCH with a high overlap of confidence intervals (Tables 2 and 4, and Figure 2). The lower bound of the confidence interval is the Halothane gene *RYR1*, which is a well known major gene for meat quality. In order to investigate if this gene is responsible for the QTL in this study, we included the gene as a fixed effect in our QTL model and repeated the analysis. The results revealed that, although *RYR1* was significant for all traits ($p < 0.01$), the QTL were still significant as well (Table 5). This indicates that *RYR1* is not the only causative gene underlying the QTL. These results support the finding of Mohrmann et al. (2006), who found also evidence for additional QTL closely linked to *RYR1* for several

fatness traits, including side fat thickness, external shoulder fat weight, belly weight and loin fat depth.

Table 5: QTL results for back fat depth (BFD), fat area (FA) and of relative number of high sized fat cells (FCH) with confidence intervals (CI), test statistics, error probabilities and order of estimated breed QTL effects – results from a model that adjusted the phenotypes for the effect of *RYR1*.

Trait	SSC	Pos	CI [a]	*F*-value	p_{add} [b]	p_{dom} [c]	p_{imp} [d]	Mode[e]	Order of effects[f]
BFB	6	100	[LIPE; A1BG] [98.3; 101.2]	3.91	0.117	0.009	0.005	(pat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
FA	6	100	[LIPE; A1BG] [98.3; 101.2]	3.99	0.002	0.096	0.006	(pat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
FCH	6	97	[S0087; TGFB1] [80.0; 99.5]	4.05	0.022	0.01	0.014	(nc)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$

[a] confidence interval (CI); [b] error probability for additive effects; [c] error probability for dominant effects; [d] error probability for imprinting effects; [e] Mode of imprinting ((pat) paternal imprinting, (nc) not consistent)), [f] $\hat{a}_P$ estimated effect of Pietrain breed, $\hat{a}_M$ estimated effect of Meishan breed, $\hat{a}_W$ estimated effect of wild boar breed.

Another candidate gene is the transforming growth factor-*β*-1 (*TGF-β-1*), which is located within the confidence intervals. In mice (Samad et al., 1997) and human (Fain et al., 2005) increased level of cytokine molecule *TGF-β-1* were found in individuals suffering from obesity. Both groups were able to detect a significant correlation between body fat content and subsequent release of *TGF-β* in subcutaneous adipose tissue. To confirm this gene as a functional candidate gene underlying the QTL found in this study, the level of *TGF-β-1* in Meishan should be compared to Pietrain, because the M breed allelic effect is higher compared to P for fat area and back fat (Table 2).

QTL results and candidate genes on SSC7

For FCL the mapped QTL in the distal region on SSC7 showed a significant imprinting effect, although the mode was not consistent (Table 4). This region contains probably the orthologue ovine chromosomal region encompassing the callipyge gene (Boysen et al., 2010), which is known to show imprinting effects in sheep. Kim et al. (2004) found several imprinting QTL for growth and meat quality traits in pigs in this chromosomal region. In contrast, Boysen et al. (2010) found an imprinted QTL for ham weight in close proximity, but not within the callipyge orthologue region.

The QTL on SSC7 for BFD and FA was also found in all other traits (SPC, MDH, FCL and FCH) with a strong overlap of confidence intervals (see also Figure 2) and a congruent

mode of inheritance, i.e. purely additive. This QTL was previously reported by other groups (e.g. de Koning et al., 2001; Meidtner et al., 2009). For BFD (Table 2) a phenomenon defined as transgressive variation (de Koning et al., 2001) is observed, i.e. M allelic effect is larger than the P allelic effect for the QTL, which is not in agreement with the breed history and the higher backfat mean of Meishan pigs. This paradox was also reported by Rohrer et al. (1998), de Koning et al. (1999) and de Koning et al. (2001). Meidtner et al. (2009) investigated peroxisome proliferator-activated receptor delta gene (*PPARD*) as a candidate gene and found *PPARD* haplotype associations with backfat thickness in a Mangalitsa x Pietrain F_2 cross. *PPARD* has been assigned between SW1856 and S0102 on SSC7 (Barbosa et al., 2004; Tanaka et al., 2006) and is located in the confidence intervals of QTL for FA, SPC, MDH, and FCH. Another candidate gene, the tumor necrosis factor alpha (*TNF-α*), is located near the maximum test statistic for these QTL. An elevated level of *TNF-α* contributes to an elevated basal lipolysis, which is typical for adipocytes of obese pigs. Several studies were conducted to investigate the effect of *TNF-α.* Knock-out mice were created (Uysal et al., 1997) and exogenous *TNF-α* was applied *in vivo* and *in vitro* to demonstrate that the *TNF-α* levels are positively correlated with the triglyceride and free fatty acid circulating level (Green et al., 1994; Souza et al., 1998). Chen et al. (2004) investigated the expression of *TNF-α* in dorsal subcutaneous tissue of Tongcheng pigs (obese) and Dabai pigs (lean). They found that *TNF-α* gene expression was significantly elevated in obese pigs and over-expressed during the development of obesity.

QTL results and candidate genes on SSC18

For the traits FA, SPC and FCL, QTL on SSC18 next to the *Leptin* locus were found. *Leptin* contributes to the regulation of appetite, and subsequently of feed intake in pigs and is secreted from adipose tissue (Ramsay and Richards, 2004). Together with insulin and growth hormone it affects the lipid syntheses (Ramsay, 2004). In a study of McNeel at al. (2000), the expression of different proteins expressed in adipocytes, among them also *Leptin*, were measured during differentiation of adipocytes. The authors found that the *Leptin* transcript concentration increased over the period of differentiation. The increase was accompanied with the increase of adipocyte size and correlated with body weight and adipocyte volume. Studies in humans showed that an increase of plasma *Leptin* concentration is associated with an increase of total body fat (Ellis and Nicolson, 1997; Jensen at al., 1999). Ramsay et al. (1998) found the same for pigs when comparing lean and obese pigs. In our study the breed allelic effect of M is large compared to W and P for the QTL for FA (Table 2), which is in good

agreement with the results of Ellis and Nicolson (1997), Jensen at al. (1999) and Ramsay et al. (1998).

Conclusions

The application of the joint QTL mapping approach applied to the powerful porcine connected F_2 crosses revealed several QTL for classical fat traits as well as for fat related cytological, metabolic and enzyme activity traits. The use of this trait combination enabled us to identify some functional and positional candidate genes underlying the QTL. These genes are involved in signalling cascades, which affect fat trait determination. Most promising candidate genes are *TNF-α* on SSC7, *IGF1* on SSC5, and *TGF-β-1* on SSC6, which need further functional investigation.

Acknowledgements

CR received funding from the H. Wilhelm Schaumann Stiftung, Hamburg, Germany, and PS from the Carl-Zeiss Stiftung, Stuttgart, Germany. The authors thank Chris Baes for language corrections.

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CHAPTER THREE

Mapping QTL for growth and muscling traits in three connected porcine F_2 crosses

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Published in:

***Archiv für Tierzucht* (2012), 55(6),** *in press*

ISSN: 0003-9438

Mapping QTL for growth and muscling traits in three connected porcine F_2-crosses

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Abstract

QTL experiments in pigs are often analysed separately, although similar or same founder breeds are frequently used to establish the experimental design. The aim of the present study was to jointly analyse three porcine F_2-crosses for six growth and four muscling traits. The crosses were a Meishan x Pietrain cross, a Wild Boar x Pietrain cross, and a Wild Boar x Meishan cross. In some cases, same founder animals were used to establish the crosses. Around 960 F_2-individuals were genotyped for around 250 genetic markers and phenotyped for birth weight, 21 and 35 day weight, slaughter weight, carcass length, food conversion ratio, ham meat weight, shoulder meat weight, loin and neck meat weight, and meat area. A multi-allele multi-QTL model was applied that estimated an additive QTL effect for each founder breed and parental origin (either paternally or maternally derived), and a dominant QTL effect for each cross. This model was previously introduced in plant breeding. Numerous QTL were mapped on the autosomes. Most QTL were localised on SSC1, 2, 3, 4, 6 and 8, and no QTL were on SSC9, 11, 13, 15, 17 and 18. The confidence intervals were short in many cases. QTL with an exceptionally high test statistic were found for carcass length on SSC1, 4, and 17. The coefficient of variation was remarkably small for this trait, which suggests that carcass length is affected by only a few genes with large effects. Positional and functional candidates underlying promising QTL are suggested for further study.

Keywords

joint analysis, QTL, growth and muscling traits

Implication

The study presented QTL results for various growth and muscling traits in pigs. The experimental design consisted of three connected F_2-crosses established from three genetically different founder breeds, i.e. Meishan, Pietrain and Wild Boar. Numerous QTL were found for all traits. QTL with an exceptionally high test statistic were found for carcass length on chromosomes 1, 4, and 17. This trait showed a small coefficient of variation, which implies that the genetic variation is due to a few genes with large effects. Promising candidate genes underlying most interesting QTL are suggested for further study.

Introduction

QTL mapping has received considerable attention in animal breeding over the last two decades. Experimental designs can be classified into two groups: those using existing family

structure, e.g. half-sib families, or those based on experimental crosses. For mapping QTL on the pig genome, F_2-experimental crosses were often established from two founder breeds (Rothschild *et al*., 2007). Although numerous F_2-designs with same founder breeds exist, they were usually analyzed separately, probably because they were established by different research groups. However, it has frequently been shown that a combined analysis of QTL experiments boosts the statistical power substantially (Walling *at al.*, 2000; Bennewitz *et al.*, 2003). The three F_2-designs established by Geldermann *et al.* (2003) are especially well suited for a joint analysis, because not only same founder breeds, but also same founder animals were used to set up the designs.

Rückert and Bennewitz (2010) proposed a model adapted from plant breeding for analysis of connected F_2-experiments and showed the benefit of a joint analysis of these three designs. It was shown that the model not only increased the statistical power in a joint analysis, but also the confidence intervals of QTL positions were remarkably small given that only linkage information was used. This model was successfully applied to map QTL for metabolic and cytological fat traits by Rückert *et al.* (2011). The aim of the present study was to map QTL for growth and muscling traits in the three F_2-designs from Geldermann *et al*. (2003) using the approach of Rückert and Bennewitz (2010).

Material and Methods

The experimental design consisted of a Meishan (M) x Pietrain (P) F_2 cross (MxP), a European Wild Boar (W) x P F_2 cross (WxP), and a WxM F_2-cross. The number of individuals in each cross and generation can be found in Table 1. Some founder animals were the same in different crosses, e.g. the same W boar was used to generate the WxP and the WxM cross. A detailed description of the design can be found in Geldermann *et al.* (2003).

Table 1: Overview of the three crosses generated by mating Meishan (M) with Pietrain (P), Wild Boar (W) with P and W with M.

Cross	M x P		W x P		W x M		∑
Sex	♂	♀	♂	♀	♂	♀	
No. of founder animals	1	8	1	9	1	4	24
No. of animal in the F_1	3	19	2	26	2	21	73
No. of animal in the F_2	170	146	150	165	169	166	966

The F_2-individuals were phenotyped for numerous traits. In this study, growth traits (birth weight, 21 day weight, 35 day weight, live weight at slaughter, food conversion ratio, and carcass length) and muscling traits (ham meat weight, shoulder meat weight, loin and neck meat weight and meat area between the $13^{th}/14^{th}$ rib in the musculus longissimus dorsi) were analysed, see Table 2.

Table 2: Traits and the abbreviations used in this paper.

Group	Trait	Abbr.	Symbols used in Figure 1
Growth	Birthweight	BW	▽
	21 day weight	W21	△
	35 day weight	W35	+
	Live weight at slaughter	SW	○
	Food conversion ratio	FCR	×
	Carcass length	CL	□
Muscling	Ham meat weight	HMW	◇
	Sholder meat weight	SMW	■
	Loin and neck meat weight	LNMW	●
	Meat area between 13th/14th rib in M.l.d	MA	▲

Data recording took place under standardised conditions at one experimental farm. The means and standard deviations of the traits in the crosses are shown in Table 3. The data were pre-corrected for the effect of the litter, the sex and age at slaughter.

Table 3: Number of observations (n), mean, standard deviation (Sd), minimum (Min) and maximum (Max) of the phenotypic observations and coefficient of variation (CV).

Trait	Cross	n	Mean	Sd	Min	Max	CV
BW	MxP	316	14,01	3,15	5,00	23,00	22,49
[kg*10]	WxP	315	14,06	2,99	5,00	26,00	21,30
	WxM	335	12,60	2,04	7,00	20,00	16,19
	Joint	966	13,54	2,84	5,00	26,00	20,97
W21	MxP	303	60,22	11,02	16,00	90,00	18,30
[kg*10]	WxP	315	45,49	12,01	14,00	81,00	26,40
	WxM	334	46,64	11,12	17,00	80,00	23,84
	Joint	952	50,58	13,16	14,00	90,00	26,02
W35	MxP	316	88,60	15,66	39,00	135,00	17,67
[kg*10]	WxP	315	68,67	16,29	28,00	116,00	23,72
	WxM	329	64,95	17,97	21,00	115,00	27,66
	Joint	960	73,96	19,63	21,00	135,00	26,55
SW	MxP	316	96,07	16,84	27,00	139,00	17,53
[kg]	WxP	314	72,37	14,62	28,00	108,00	20,20
	WxM	335	71,16	13,79	23,00	107,00	19,38
	Joint	965	79,71	18,94	23,00	139,00	23,76
CL	MxP	316	91,33	6,08	63,50	106,00	6,66
[cm]	WxP	315	79,89	5,19	62,50	94,00	6,50
	WxM	335	78,21	5,40	56,00	92,50	6,90
	Joint	966	83,05	8,05	56,00	106,00	9,69
FCR	MxP	316	3,88	0,88	2,60	11,46	22,59
[kg/kg]	WxP	315	3,42	0,50	2,54	8,83	14,66
	WxM	335	4,32	0,68	2,81	7,03	15,64
	Joint	966	3,88	0,79	2,54	11,46	20,38
HMW	MxP	316	7,09	1,26	2,00	11,20	17,78
[kg]	WxP	315	6,58	1,33	2,60	10,70	20,25
	WxM	335	4,44	0,76	1,55	6,35	17,08
	Joint	966	6,00	1,62	1,55	11,20	27,02
SMW	MxP	316	3,64	0,63	1,15	5,65	17,25
[kg]	WxP	315	3,27	0,67	1,30	5,35	20,51
	WxM	335	2,41	0,45	1,00	3,90	18,53
	Joint	966	3,09	0,78	1,00	5,65	25,34
LNMW	MxP	316	6,48	1,17	1,70	10,10	18,11
[kg]	WxP	315	5,55	1,26	1,95	10,05	22,65
	WxM	335	3,82	0,70	1,30	6,05	18,32
	Joint	966	5,25	1,54	1,30	10,10	29,28
MA	MxP	316	29,29	5,35	14,56	49,31	18,26
[cm*cm]	WxP	313	32,71	6,40	12,93	50,05	19,57
	WxM	335	19,42	3,13	7,73	31,81	16,13
	Joint	964	26,97	7,64	7,73	50,05	28,32

All animals were genotyped for around 250 genetic markers (mostly microsatellites). These marker data were linked to the pedigree and a common genetic map was calculated and presented by Rückert and Bennewitz (2010). Because many markers were genotyped in two or three crosses this calculation was straightforward. QTL analysis was done using the multi-allele multi-QTL model of Rückert and Bennewitz (2010). The model assumes that two founder breeds *i* and *j* of an F_2 individual are divergent homozygous at a putative QTL. Under this assumption, for each F_2 individual and each chromosomal position (i.e. each cM) the following four genotype probabilities were estimated, $pr(Q_i^p Q_i^m)$, $pr(Q_j^p Q_i^m)$, $pr(Q_i^p Q_j^m)$ and $pr(Q_j^p Q_j^m)$, using a modified version of BigMap (Reinsch, 1999). The upper subscripts denote the parental origin of the alleles (i.e. paternally (*p*) or maternally (*m*) derived) and the lower subscripts denote the breed origin of the alleles (i.e. breed *i* or *j*, with *i*, *j* being breed M, P, or W). These probabilities were used in a regression framework to estimate an additive QTL effect for each founder breed and each parental origin, i.e. $\hat{a}_M^p, \hat{a}_M^m, \hat{a}_P^p, \hat{a}_P^m, \hat{a}_W^p, \hat{a}_W^m$, where the lower subscript denotes the breed and the upper subscript denotes the parental origin. Additionally, a dominant QTL effect was estimated for each cross. The model was fitted for each cM on the autosomes. The test statistic was an F-test. The null hypothesis was that every estimate (i.e. each additive and dominant QTL effect estimated) at the position with the highest test statistic on a chromosome was equal to zero. The alternative hypothesis was that at least one effect was different from zero at this position. Correction for multiple testing on a chromosome was done using the quick method of Piepho (2001), accepting a 5% error probability for significance. This somewhat loose threshold value was chosen because it was shown that many QTL with small effects segregate in these crosses (Bennewitz and Meuwissen, 2010). At significant chromosomal positions it was tested if the additive and / or the imprinting and / or the dominant QTL effect were significant. These tests were conducted by building linear contrasts and resulted in the three error probabilities p_{add}, p_{dom}, and p_{imp} for additive, dominance and imprinting QTL, respectively. Additionally, the number of QTL alleles was determined based on their mendelian effects (i.e. ignoring parental origin of the alleles). QTL confidence intervals were obtained by the one LOD drop method (Lynch and Walsh, 1998). For this purpose, *F*-values were converted into LOD-scores. Multiple QTL were included as cofactors in the model using a forward selection approach. This increased statistical power and enabled the detection of multiple QTL on a chromosome. A more detailed description of this procedure can be found in Rückert and Bennewitz (2010).

Results and discussion

The summary statistics in Table 1 reveal substantial variation for all traits within and across the three crosses. However, a low coefficient of variation was observed for CL. For the growth traits W21, W35 and CL, and SW the mean of the MxP cross is substantially higher than the mean of the other two crosses. For BW, HMW, and MA the WxM cross mean is substantially lower. This is in agreement with the history of the breeds. The P breed is a typical sire line used to generate crosses for slaughter pigs, and was selected for growth and meat quality during the last decades. The M breed is known to be a fatty and fertile breed. W is a small size breed. It was not subject to artificial selection and hence little or no selection pressure was on growth traits. The QTL results for growth traits and muscling traits are shown in Table 4 and 5, respectively. For many QTL with significant additive effects three mendelian alleles could be observed. In this case, the order of effects was often, but not always, $\hat{a}_P > \hat{a}_M > \hat{a}_W$. If only two mendelian alleles were observed, the order of effects was often $\hat{a}_P = \hat{a}_M > \hat{a}_W$, or $\hat{a}_P > \hat{a}_M = \hat{a}_W$. This was expected due to the selection history of the breeds mentioned above, but it also indicates genetic variation for these traits within the founder breeds.

Table 4: QTL results for growth traits.

Trait	SSC	Pos	CI [a]		*F*-value	p_{add} [b]	p_{dom} [c]	p_{imp} [d]	Mode[e]	Order of effects[f]
BW	8	6	[0.0; [SW905;	18.0] SW933]	3.97	0.0005	0.0172	0.1980	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
W21	6	101	[96.4; [RYR;	106.0] SKI]	4.62	0.0017	0.0050	0.1273	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	8	3	[0.0; [SW905;	18.0] SW933]	3.99	<0.0001	0.1194	0.6099	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	15	99	[71.9; [SW2053;	99.4] SW1983]	3.27	0.6207	0.0150	0.0030	(nc)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	16	10	[0.0; [S0111;	33.3] SW419]	3.24	0.0327	0.0363	0.0139	(nc)	$\hat{a}_W > \hat{a}_M = \hat{a}_P$
W35	6	100	[96.4; [RYR;	106.0] SKI]	4.21	0.0014	0.0152	0.1513	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	8	5	[0.0; [SW905;	34.0] SW933]	3.82	<0.0001	0.0393	0.8651	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	12	1	[0.0; [S0143;	10.8] EAD]	3.22	0.7210	0.0748	0.0006	(mat)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	12	75	[64.5; [SW874;	99.3] S0174]	3.45	0.2497	0.0577	0.0016	(nc)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	14	132	[105.1; [SW2488;	151.3] SW2515]	2.60	0.0081	0.0544	0.9052	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
SW	1	90	[77.3; [SW2130;	104.1] IGFR]	7.99	<0.0001	0.9368	0.0118	(nc)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	2	76	[70.6; [MYOD1;	78.3] INSR]	4.84	<0.0001	0.0095	0.3624	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	3	59	[50.8; [OIF;	74.0] SW828]	3.18	0.0205	0.0038	0.6224	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	4	71	[62.1;	75.3]	5.62	<0.0001	0.1687	0.4926	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$

	5	156	[SW1073; S0073] [110.0; 157.9] [IGF1; SW967]	3.76	0.6173	0.6432	<0.0001	(mat)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	6	85	[73.7; 94.4] [FTO; ETH5001]	3.43	0.0036	0.0573	0.0700	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	7	63	[0.0; 73.3] [S0025; CYPD]	3.56	<0.0001	0.2359	0.4437	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	8	12	[0.0; 34.0] [SW905; SW933]	5.18	<0.0001	0.2696	0.0707	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
CL	1	110	[77.3; 119.2] [SW307; S0082]	3.73	0.0873	0.0248	0.0021	(mat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	1	161	[149.6; 178.5] [TGFBR1; SW705]	9.26	<0.0001	0.1989	0.2241	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	3	58	[35.9; 74.0] [S0206; SW828]	3.63	0.1496	0.0005	0.3775	(- -)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	4	73	[62.1; 81.0] [SW1073; CASQ1]	9.45	<0.0001	0.0053	0.0424	(nc)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	7	73	[61.3; 75.2] [ID4_ECO; KE6]	15.32	<0.0001	0.1573	0.2116	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	8	13	[0.0; 34.0] [SW905; SW933]	3.89	<0.0001	0.4477	0.2922	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	10	65	[52.5; 74.1] [SW497; GAS1]	3.03	0.1906	0.1264	0.0083	(mat)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
FCR	1	105	[77.3; 119.2] [SW2130; S0082]	4.23	0.0856	0.0018	0.0105	(mat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	3	41	[11.6; 74.0] [SW72; SW828]	3.46	0.0021	0.0605	0.7272	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	6	99	[80.0; 102.4] [S0087; EAH]	3.25	0.0003	0.1463	0.9540	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$

[a] confidence interval (CI); [b] error probability for additive effects; [c] error probability for dominant effects; [d] error probability for imprinting effects; [e] Mode of imprinting ((--) imprinting not significant, (mat) maternal imprinting, (pat) paternal imprinting, (nc) not consistent)), [f] $\hat{a}_P$ estimated effect of Pietrain breed, $\hat{a}_M$ estimated effect of Meishan breed, $\hat{a}_W$ estimated effect of Wild Boar breed.

Table 5: QTL results for muscling traits.

Trait	SSC	Pos	CI [a]		*F*-value	p_{add} [b]	p_{dom} [c]	p_{imp} [d]	Mode[e]	Order of effects[f]
HMW	1	66	[43.5; SWR2300;	77.3] SW2130	5.81	<0.0001	0.9619	0.0899	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	1	119	[110.3; SW307;	126.3] SW780	3.36	0.0004	0.1097	0.2797	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	2	34	[14.9; SW2623;	68.0] MLP	4.23	0.0080	0.7878	0.0006	(mat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	3	0	[0.0; SERPINE1;	11.6] SW72	3.94	<0.0001	0.6002	0.3853	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	4	71	[62.1; SW1073;	75.3] S0073	6.95	<0.0001	0.2454	0.2363	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	5	120	[110.0; IGF1;	150.4] MYF5	5.18	0.0002	0.9961	<0.0001	(mat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	6	98	[80.0; S0087;	106.0] SKI	5.76	<0.0001	0.3880	0.2407	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	7	73	[61.3; ID4_ECO;	86.5] S0102	4.06	<0.0001	0.5281	0.4518	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	8	15	[0.0; SW905;	34.0] SW933	5.49	<0.0001	0.4905	0.3259	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	10	63	[52.5; SW497;	74.1] GAS1	5.03	0.0723	0.0052	0.0003	(mat)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	12	95	[51.0; S0083;	109.8] S0106	2.85	0.0037	0.3635	0.0770	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	14	91	[78.0; ACTA1;	105.1] SW2488	6.12	0.0001	0.5692	0.6072	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
SMW	1	119	[110.3; SW307;	126.3] SW780	5.39	<0.0001	0.1457	0.0350	(pat)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	2	48	[0.0; SW2443;	77.8] UBL5	4.44	0.0001	0.5542	0.0107	(nc)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	3	0	[0.0; SERPINE1;	11.6] SW72	4.73	<0.0001	0.1081	0.6617	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	3	56	[35.9; S0206;	74.0] SW828	3.40	0.0993	0.0007	0.5296	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	4	68	[62.1; SW1073;	75.3] S0073	8.98	<0.0001	0.4658	0.2340	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	5	120	[77.3; S0005;	150.4] MYF5	3.69	0.0043	0.9294	0.0011	(mat)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	6	72	[58.1; SW1057;	80.0] S0087	3.90	0.0024	0.1828	0.0106	(mat)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	7	70	[61.3; ID4_ECO;	86.5] S0102	6.98	<0.0001	0.5094	0.1476	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	8	12	[0.0; SW905;	34.0] SW933	5.67	<0.0001	0.3958	0.6961	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	10	65	[30.6; SW443;	74.1] GAS1	3.75	0.2838	0.1446	0.0004	(mat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
LNMW	1	66	[43.5; SWR2300;	77.3] SW2130	7.10	<0.0001	0.9358	0.1127	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	1	119	[110.3; SW307;	126.3] SW780	1.93	0.0336	0.1941	0.5139	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	1	162	[149.6; TGFBR1;	178.5] SW705	3.28	0.0121	0.0133	0.1105	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	2	25	[5.2; SWC9;	52.9] SW240	3.36	0.0033	0.1639	0.1554	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	3	55	[35.9; S0206;	74.0] SW828	4.65	0.0003	0.0006	0.9149	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	4	71	[50.9; SW2128;	75.3] S0073	7.33	<0.0001	0.2312	0.2368	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	5	118	[92.3; SW152;	150.4] MYF5	3.69	0.0046	0.8156	0.0011	(nc)	$\hat{a}_W > \hat{a}_M = \hat{a}_P$

	6	88	[80.0; 99.5]	[S0087; TGFB1]	4.91	<0.0001	0.0385	0.2132	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	8	13	[0.0; 34.0]	[SW905; SW933]	4.89	<0.0001	0.2773	0.1846	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	10	61	[30.6; 74.1]	[SW443; GAS1]	3.97	0.6031	0.0090	0.0006	(nc)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	14	65	[43.8; 105.1]	[SW2038; SW2515]	3.70	0.0070	0.0031	0.2850	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
MA	1	160	[144.7; 178.5]	[TPM2; SW705]	5.74	<0.0001	0.4987	0.0042	(pat)	$\hat{a}_P > \hat{a}_W > \hat{a}_M$
	2	4	[0.0; 14.9]	[SW2443; SW2623]	4.72	0.0049	0.0019	0.0053	(mat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	4	71	[62.1; 75.3]	[SW1073; S0073]	4.27	<0.0001	0.9746	0.6095	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	6	94	[80.0; 99.5]	[S0087; TGFB1]	4.65	<0.0001	0.0444	0.2910	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	8	23	[0.0; 49.4]	[SW905; SW1070]	4.31	<0.0001	0.2301	0.1895	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	8	96	[49.4; 110.1]	[SW1070; SW16]	3.04	0.0164	0.0095	0.6006	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	14	77	[60.7; 105.1]	[SW540; SW2488]	5.69	<0.0001	0.5742	0.5435	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$

[a] confidence interval (CI); [b] error probability for additive effects; [c] error probability for dominant effects; [d] error probability for imprinting effects; [e] Mode of imprinting ((--) imprinting not significant, (mat) maternal imprinting, (pat) paternal imprinting, (nc) not consistent)), [f] $\hat{a}_P$ estimated effect of Pietrain breed, $\hat{a}_M$ estimated effect of Meishan breed, $\hat{a}_W$ estimated effect of Wild Boar breed

Most of the QTL were found on SSC1, 2, 3, 4, 6 and 8, and no QTL were on SSC9, 11, 13, 15, 17 and 18 (Figure 1).

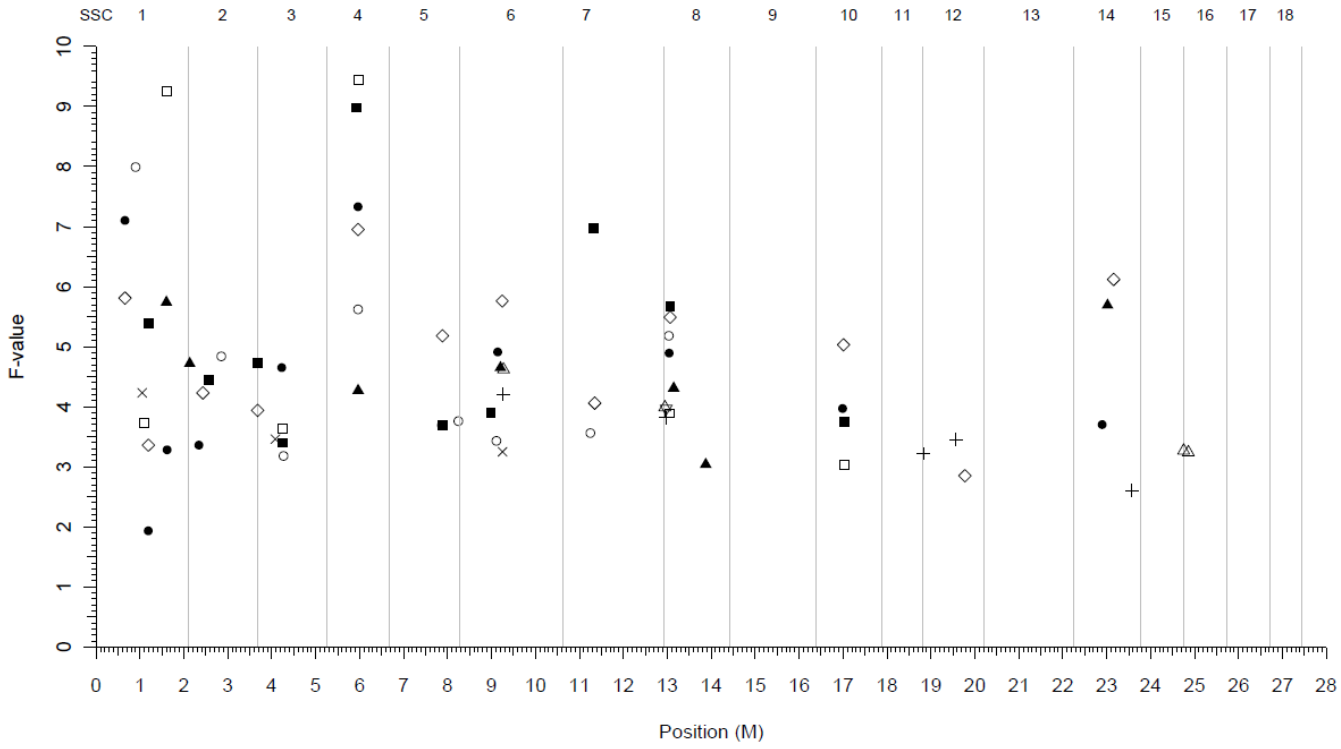

Figure 1: Overview of the QTL distribution of the porcine genome. Note that the test statistic of the QTL for CL on SSC7 was F>15 (not shown in the figure). The definition of the symbols is given in Table 2.

For the six growth traits, a total of 28 QTL were found, 12 with a significant dominant QTL effect and 10 with a significant imprinting QTL effect. For the four muscling traits, 40 QTL were found, with 10 and 12 significant dominant and imprinting effects, respectively. Most QTL were significant due to their additive effects. Some QTL, however, showed only a significant dominant and/or a significant imprinting effect, but no significant additive effects. For example, see QTL on SSC3 for CL and SMW, SSC5 for SW, SSC10 for HMW and SMW and SSC12 for W35. Consequently, no different mendelian alleles could be observed for these QTL, i.e. $\hat{a}_P = \hat{a}_M = \hat{a}_W$. Many QTL showed similar position estimates and overlapping confidence intervals. The QTL with significant imprinting effects were mainly located on chromosomes 1, 2, 5 and 10. The mode of imprinting (paternal or maternal) was not always consistent across the three crosses. This can be interpreted as evidence against real imprinting effects, because it is not likely that an imprinted gene has a different mode in different crosses. As discussed in detail by Rückert and Bennewitz (2010), the test for imprinting as conducted in this study might also reveal significance due to within founder breed segregation rather than due to real imprinting.

Due to the high number of mapped QTL not all of them will be discussed. A comparison of the results and other literature results can be done using the pig QTL data base (Hu *et al.,* 2005). In the following, some interesting chromosomal regions will be considered and putative candidate genes underlying the QTL will be discussed.

For all traits except BW, W21, and W35 one or two QTL were found on SSC1. These QTL were distributed over five confidence intervals (see also the plots of the test statistics in Figure 2). QTL affecting growth and muscling on this chromosome have previously been mentioned in other F_2 cross-studies (Bidanel *et al.*, 2001; Milan *et al.,* 2002), although the QTL were not always located at the same region as in this study.

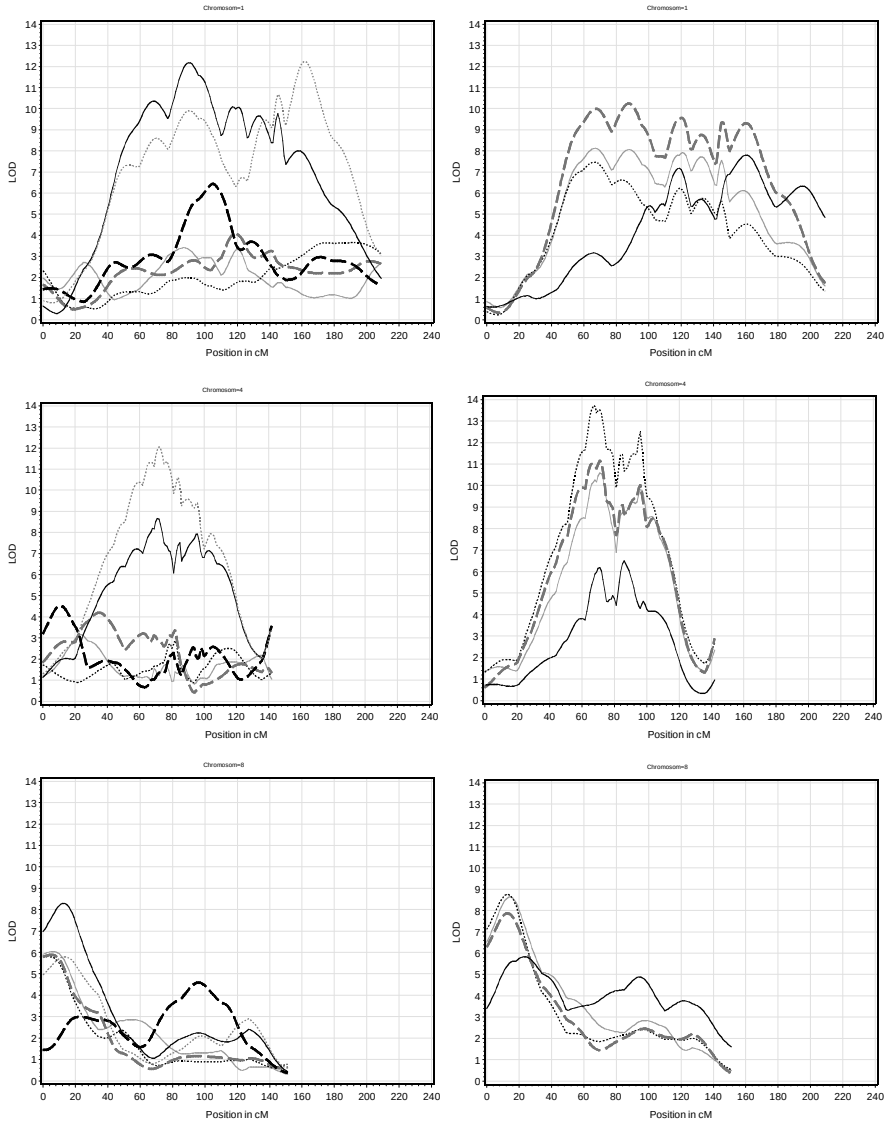

Figure 2: Plot of the test statistics for Chromosome 1 (top), 4 (middle) and 8 (bottom). Plots on the left show growth traits (gray solid=BW, black dotted=W21, gray dashed=W35, black solid=SW, black

dashed=CL, gray dotted=FCR) and those on the right show muscling traits (gray solid=HMW, black dotted=SMW, gray dashed=LNMW, black solid=MA).

QTL were found for all muscling traits on SSC2. This is in agreement with Varona *et al.* (2002). A maternal imprinting effect was found for HMW and MA. The confidence intervals of these two QTL contain the *IGF2* locus (co-localized with the microsatellite SWC9) which affects muscling and fattening traits and is known to be imprinted (Nezer *et al.,* 1999). However, due to the large confidence intervals it might be that these imprinted QTL are caused by other imprinted genes, e.g. *INS2* (Jeon *et al.*, 1999). For SW a QTL was mapped in the interval between *MYOD1* and *InsR*. Varona *et al.* (2002) also found significant QTL in this chromosomal region. *MYOD1* is known to be involved in muscle differentiation and is mentioned as a candidate gene for growth (Fan *et al.*, 2011).

QTL for some growth and muscling traits were found at the distal part of SSC3, with the *SERPINE1* gene at the start of the confidence intervals. It codes for a protein called Serpine1, which is a molecule located in the extracellular space and is known to influence obesity and diabetes in humans (Kaur *et al.*, 2010). *SERPINE1* may be seen as possible candidate gene for growth. Additional QTL with a highly significant dominance effect were found for SW, CL, FCR, and LNMW.

The SSC4 is known as the chromosome with the highest density of QTL in pigs (Rothschild *et al*., 2007). In our study QTL were found for every trait, with a remarkably consistent chromosomal position estimated in the centromeric region (see also Figure (2)). In this interval two markers located in the gene coding regions of *VATP* (coding for the vacuolar ATPase proton pump) and *ATP1B1* (coding for the sodium/potassium-dependent ATPase beta-1 subunit) are of interest. Both gene products are involved in the ATP-dependent pathway including protein synthesis. This interval region is already known through meta-QTL analyses (Silva *et al*. (2011)).

Several QTL were found on SSC5 with highly significant imprinting effects and a consistent mode of imprinting, i.e. maternally imprinted. The confidence intervals included *IGF1*, which is known to be involved in a wide variety of growth responses (Fan *et al.*, 2011) and has been suggested as a candidate gene (Roehe *et al.* (2003)).

Porcine chromosome 6 is frequently mentioned in QTL studies, because several genes, such as the *RYR1* gene associated with pale, soft and exudative meat and *TGF-β-1*, which controls cell growth, cell performance and cell differentiation, are located there. These two markers are within the overlapping QTL confidence intervals for six traits in our study. Additionally, Fan *et al.* (2009) detected a polymorphism within the fat mass and obesity associated protein gene (*FTO*), which is associated with growth and fatness traits. This gene is located at the bound of the QTL confidence intervals for SW and SMW in our study.

An exceptionally high test statistic (F-value ~15) was found for a QTL for CL on SSC7. For this trait two other highly significant QTL (F-value >9) were also found. These high test statistic values were not observed for other traits. It seems that the low variation observed for CL is due to only a few genes with large effects. One possibly explanation might be that the genes affect the number of ribs. Therefore, candidate genes involved in determination of rib number were investigated. Kingsley *et al.* (1992) demonstrated that the short ear locus, located close to, but not within the confidence interval of CL on SSC7, contains the *Bmp5* gene. Among others, Kingsley *et al.* (1992) demonstrated that null mutations at the *Bmp5* locus reduce the number of ribs along the vertebral column. Although not included in the confidence interval, the *Bmp5* locus should be considered in further studies to unravel this exceptional QTL result.

Nine QTL were found on SSC8 (see Figure (2)). In most cases the QTL were located in the distal region around the peroxisome proliferative activated receptor gamma coactivator 1 (*PGCMUT* or *PPARGC1*). *PPARGC1* is a candidate gene that regulates the determination of myofibre types and has an important influence on myofibre growth (Jiang *et al.*, 2011). In the study of Jiang *et al.* (2011), strong differences in gene expression between Landrace pigs and Chinese Meishans were reported. The detected QTL on SSC10 were all located in one region near the growth arrest-specific protein 1 marker (*GAS1*). *GAS1* is an integral membrane protein and plays an important role in growth suppression in humans and mice (Del Sal *et al.*, 1994).

The three QTL for muscling identified on SSC14 are located in the region around the marker actinin alpha 2 (*ACTN2*) and actin alpha 1 (*ACTA1*). Davoli *et al.* (2003) searched for polymorphisms in the myopalladine (*MYOP*) gene and placed the porcine MYOP gene, which is closely linked to ACTA1, on the genetic map of SSC14. Myopalladin (*MYOP* or

FLJ14437) is a 145-kDa sarcomeric protein, which binds α-actinin with nebulin in skeletal muscle and functions in the organization and assembly of the Z-line (Bang *et al.*, 2001). Due to its role as a skeletal muscle gene especially coding for a sarcomeric protein, MYOP may plays a key role in muscle mass accretion. Wimmers *et al.* (2007) searched for associations between functional candidate genes derived from gene-expression profiles of prenatal porcine muscle tissue and meat quality and muscle deposition. For *MYOP* the authors were able to show association with ham weight and lean content.

Conclusion

In this study the three connected F_2-designs of Geldermann *et al.* (2003) were analysed jointly for muscling and growth traits using a multi-allele multi-QTL model. A large number of QTL was found compared to the separate analysis of crosses (see Geldermann *et al.*, 2003). This underlines the high statistical power resulting from analysing the data jointly using an appropriate model. Based on small and overlapping confidence intervals, positional and functional candidate genes were suggested for most interesting QTL regions. In particular, the exceptional QTL for carcass length should be further investigated.

Acknowledgements

CR received funding from the H. Wilhelm Schaumann Stiftung, Hamburg, Germany, and PS from the Carl-Zeiss Stiftung, Stuttgart, Germany. The authors thank Chris Baes for language corrections.

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GENERAL DISCUSSION

The general aim of the thesis was the re-analysis of three connected F2 crosses generated by Geldermann et al. (2003). For this propose, a statistical model that is able to jointly analyse the three F2-crosses was developed. It was adapted from plant breeding and was extended to account for imprinting. The model was implemented in a computationally fast multiple framework.. This enabled us to analyse numerous traits recorded for the F2-individuals. The model was applied and compared to the standard QTL model. It was shown that the joint analysis of the three connected F2-crosses led to a substantial additional power, to a higher number of significant QTL, and in some cases to very short confidence intervals. The aim of this section is to discuss some additional aspects of the experimental design, the distribution of the QTL effects, the phenomena of epitasis and finally the use of marked QTL in marker assisted breeding schemes.

Experimental design:

As stated in the previous chapters, the experimental design of the study was based on the founder breeds Pietrain (P), Meishan (M) and Wild Boar (W). To some extent not only the same founder breeds but also the same founder animals were used to establish the three crosses. The experimental design was set up in the 1990s. At that time, microsatellites were the markers of choice. Microsatellites are spread more or less evenly throughout the genome and they are, to some extent, highly polymorphic, showing five to ten distinct alleles within the crosses in the study. The F2-individuals were genotyped for around 250 microsatellites. Clearly this number of markers is not high enough to ensure linkage disequilibrium within the breed. Therefore, linkage disequilibrium, which is essential for mapping QTL, was generated by the establishment of the F2-crosses. This resulted in long range linkage disequilibrium blocks. In the area of genomics, microsatellites have been replaced by single nucleotide polymorphism (SNP) markers. The discovery of SNP markers is a by-product of sequencing projects of the species. The pig genome was sequenced in the year 2009 and the length of the genome is around 2.2 giga bases (Eggen, 2010). Subsequently a porcine SNP chip was generated which included 62,000 SNP markers. The use of this SNP chip would enable mapping QTL within a segregating population, because it can be postulated that many QTL are in linkage disequilibrium with at least one of these SNPs. The general strategy for genome wide association analyses using SNP chips in livestock breeds is reviewed by Goddard and Hayes (2009). Nevertheless, QTL results obtained within this study are a valuable source of

information and will provide additional evidence where casual mutations located on the genome, and hence the genes affecting the traits, are underlying the QTL.

QTL effects and distributions:

In the original analysis of these three crosses conducted by Geldermann et al. (2003), only additive and dominant gene actions were considered. In a subsequent study conducted by Bennewitz and Meuwissen (2010), the distribution of the additive effects and the dominant coefficient, which is defined as a dominant deviation divided by the absolute additive effect, was calculated. The additive effects showed an exponential distribution, meaning that there are only a few QTL of large effects and many QTL with small effects. This is in agreement with other published results (Hayes und Goddard, 2001). The distribution of the dominant coefficient was normal with a positive mean. This shows that dominance is the rule rather than the exception and is also in agreement with more general research on the phenomenon of dominance. More precisely, the positive mean (the heterozygote genotype is closer to the homozygote genotype) which produces a higher phenotype, is a consequence of hyperbolic relationship between the amount of end product and enzyme activity. This relationship is formalised in the well known Kacser-Burns model (Kacser and Burns, 1981). Furthermore, selection is responsible for the observed phenomenon that heterozygote genotypes are generally closer to the homozygote genotypes with high end product; more details can be found in Keightley (1996), Bourguet (1999) and Wellmann and Bennewitz (2011). In this study imprinting was also included in the model, and many QTL with a significant imprinting effect were found. Until now no distribution was derived for imprinting effects. In principle, the method of Bennewitz and Meuwissen (2010), i.e. the use of a mixture of normal distributions which account for heterogeneous error variance of estimates, could be used to derive the distribution of imprinting effects. However, in this thesis no attempts were made to derive these kinds of distributions for imprinting. It can be assumed that not all significant imprinting QTL show a real imprinting effect, i.e. the number of imprinting QTL is inflated. This inflation might be due to the within-founder line segregation of the QTL. The model applied in this thesis is based on the assumption that founder lines are divergent homozygote at the QTL, and within-founder segregation of the QTL might erroneously result in an imprinting effect (de Koning et al., 2000). Nevertheless, many imprinted QTL were found in well-known imprinting clusters on chromosome 2 and the mode of imprinting was consistent across the three crosses, i.e. the mode was paternal or maternal imprinted in all three crosses.

This can be seen as evidence for real imprinting rather than statistical artefacts and underlines the importance of modelling imprinting.

Epitasis:

Epitasis in its general form describes any statistical interaction between two or more loci. In two-locus epitasis, the following interaction effects might occur: interaction between both additive effects, interaction between additive and dominance effects, interactions between dominance and additive effects and interactions between dominance and dominance effects. If imprinting is included, the imprinting effect of the first QTL can interact with additive, dominance and imprinting effects of the second QTL and vice versa. An attempt was made to extend the model introduced in chapter one for the phenomena of epitasis. In the extension of the model, special emphasis was put on the orthogonality of the model. This means that the definition of the additive, dominance and imprinting effects are the same, whether other QTL and interactions are fitted into the model or not (see also Alvarez Castro and Carlborg, 2007). This orthogonality was ensured by using appropriate design matrices. A preliminary application of the extended model revealed some dependencies between interaction effects which need further investigation (Rückert and Bennewitz, unpublished). As an alternative, a model was applied to test for pair-wise epistatic effects of previously mapped significant QTL within the crosses. This model generally followed the framework of Wolf and Cheverud (2009), leading to nine orthogonal forms of epistatic effects for each cross. This model was applied to meat quality traits and revealed three point-wise and one experimental-wise significant interaction effects (Stratz et al., 2011). Opinions on the importance of epitasis in animal breeding differ. Hill et al. (2008) argue that most of the genetic variance is due to additive genetic gene action and not so much due to dominance and epitasis. The reason is that gene frequencies generally follow a U-shaped distribution and hence the variance of interacting gene effects cannot be so large. Carborg and Haley (2004) argued that epistatic effects are too often neglected in the analysis of QTL experiments and they gave some evidence that QTL epistatic effects are often but not always observable. These apparent conflicting opinions can be overcome if the gene frequencies in the experimental population are considered. Hill et al. (2008) argued from a segregating population point of view, where the gene frequencies are U-shaped distributed and hence the variance explained by epitasis is naturally small. Carborg and Haley (2004) argue from a F2-cross point of view, where the gene frequency is moderate (around 0.5) and the variance explained by epitasis reaches a much higher level compared to that of segregating populations. Nevertheless, an analysis of

the data of this thesis with respect to epistatic effects might contribute to detection of interacting genes, regardless if they explain much of genetic variance in segregating populations or not.

Use of QTL in livestock breeding:

As stated in the introduction, one of the main goals of mapping QTL was to include the mapped QTL in so-called marker assisted breeding schemes. It was shown that the advantage of these marker assisted selection (MAS) breeding schemes is highest if the generation interval is long, if the trait has a low heritability or if it is difficult to measure the trait, for instance if the trait is sex limited (Meuwissen and Goddard, 1996). Following this, there were some high expectations in the prospects of marker assisted breeding schemes. However, only few breeding schemes included QTL as selection criteria (Dekkers, 2004). The reason is that the number of mapped QTL is relatively low compared to the total number of segregating QTL in the population and the variance explained by these QTL is limited. Other reasons include difficulty in the implementation of marker assisted breeding value estimation and MA-BLUP. The QTL results obtained in F2-crosses cannot be directly used in marker assisted breeding schemes, because selection does not take place in F2-crosses but in founder lines. In mapping QTL in F2-crosses it is assumed that the founder lines are divergent homozygote at the QTL. Thus, if a QTL is mapped with a high probability, the QTL is fixated in one of the founder lines and selection can not act on the marked QTL in the founder line. The idea of marker assisted selection was replaced by genomic selection, which relies on linkage disequilibrium and was first introduced by Meuwissen et al. (2001). Genomic selection is based on the following steps. The first step: a reference population is phenotyped for the traits of interest and genotyped for a SNP chip. In this reference population, marker effects are estimated using G-BLUP methods or Bayesian methods. In the second step selection candidates, which are usually young animals, are genotyped for the SNPs and the marker effects which were estimated in step one are summed up for these individuals. This results in the direct genomic value. The direct genomic value is combined with the conventional BLUP breeding value using selection index theory (vanRaden, 2009). This combination results in the genomic enhanced breeding value or short genomic estimated breeding value. Selection candidates are selected based on the genomic breeding value. This genomic selection technique was introduced successfully in many dairy breeding populations. It works by reducing the generation interval from around six years to two to three years (Schaeffer, 2006). In pig breeding, prospects of genomic selection are not as advantagous

compared to dairy cattle breeding. The reason is that it is difficult to obtain a reference population of sufficient size and hence the estimated marker effects show higher errors compared to the marker effects estimated in dairy cattle. Furthermore, the generation interval is already on a lower level compared to dairy cattle. Nevertheless, first breeding organisations are on the way to implement genomic selection in their populations. In sire line pig breeding, first results of genomic selection are presented by Bennewitz et al. (2011).

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GENERAL SUMMARY

Mapping Quantitative Trait Loci (QTL) has received considerable attention in livestock genetic research over the last two decades. Knowledge of the location, the mode of inheritance and the size of effects of QTL contribute to a deeper understanding of the genetic architecture of quantitative or complex traits. Furthermore, mapped QTL were envisaged for use in so-called marker assisted selection programs. Before the era of genomics started, microsatellites were usually used as genetic markers for QTL mapping.

In pigs, F_2-crosses were frequently established from divergently selected founder breeds. Usually, the sizes of these F_2-experiments are in the range of 300 individuals, which is too small to obtain sufficient statistical power to map QTL precisely.

One large F_2-experiment was set up in the 90th of the last century at the University of Hohenheim. Three F_2-crosses from three genetically different founder breeds (Meishan, Pietrain and European Wild Boar) with almost 1000 individuals were genotyped and phenotyped for around 50 quantitative traits. In further studies, each of the crosses were analysed separately and more complex modes of inheritance were ignored. However, several researchers showed that a combined analysis with several QTL experiments can boost statistical power. Additionally, the mode of inheritance is sometimes not restricted to additive and dominant gene action. The overall aim of this thesis was the joint analysis of these three F_2-crosses with more appropriate statistical models and to draw more precise conclusions about the QTL segregating within these experimental designs.

In **CHAPTER ONE** a statistical model tailored to jointly analyse the three crosses was developed. It was adapted from plant breeding and extended to account for imprinting. Using the model an additive QTL effect for each founder breed allele and a dominant QTL effect for each combination of alleles derived from different founder breeds were estimated. Multiple QTL, multiple QTL alleles and imprinting effects were considered. This model was compared to a standard QTL model frequently used in mapping QTL in F_2-crosses, which analysed each cross separately. The following traits were considered for this comparison: daily gain, back fat and carcass weight. Substantial phenotypic variation was observed within and between crosses. For daily gain, back fat and carcass weight, 13, 15 and 16 QTL were found, respectively. For back fat, daily gain and carcass weight, respectively three, four, and five loci showed significant imprinting effects. The number of QTL mapped was much higher than when each design was analysed separately. Additionally, the test statistic plot along the

chromosomes was much sharper leading to smaller QTL confidence intervals. In many cases, three QTL alleles were observed. The statistical power was high because of the reduced number of estimated parameters and the large number of individuals. The applied model was flexible and was computationally fast.

In **CHAPTER TWO** the known model was applied to several fat related traits measured in the same F_2-design. Fat traits are frequently included as a goal of pig breeding programmes. Many QTL mapping experiments have been conducted to find loci affecting fat traits and numerous QTL have been reported. Most studies used fat traits defined in a rather classical way, e.g. back fat thickness or intramuscular fat. These traits can be seen as end products within a cascade of physiological steps, which are controlled by gene products like enzymes. For the interpretation of QTL results and the identification of genes and pathways underlying the QTL it might be advantageous to have some trait measurements of the direct gene products. Therefore, metabolic, enzymatic and cytological fat traits were used. The traits investigated were back fat depth and fat area as well as relative number of fat cells with different sizes, soluble protein content as an indicator for the level of metabolic turnover and NADP-malat dehydrogenase as an indicator for enzyme activity. The results revealed significant QTL on chromosomes 1, 2, 4, 5, 6, 7, 8, 9, 14, 17 and 18, with often an overlap of confidence intervals of several traits. These confidence intervals were in some cases remarkably small, which is due to the high statistical power of the design. A substantial proportion of QTL showed significant imprinting effects. The small and overlapping confidence intervals for the classical fatness traits as well as for the cytological, enzymatic and metabolic traits enabled positional and functional candidate gene identification for several mapped QTL.

Muscling and growth traits are normally included in pig breeding programmes, especially in sire line pig breeding. Therefore, in the **CHAPTER THREE** the above mentioned model was used to map QTL for muscling and growth traits collected in the F2-crosses of the University of Hohenheim. The traits were: birth weight, 21 and 35 day weight, slaughter weight, carcass length, food conversion ratio, ham meat weight, shoulder meat weight, loin and neck meat weight, and meat area. Numerous QTL were mapped on the autosomes. Most QTL were localised on SSC1, 2, 3, 4, 6 and 8, and no QTL were on SSC9, 11, 13, 15, 17 and 18. The confidence intervals were short in many cases. QTL with an exceptionally high test statistic were found for carcass length on SSC1, 4, and 17. The coefficient of variation was

remarkably small for this trait, which suggests that carcass length is affected by only a few genes with large effects. Positional and functional candidates underlying promising QTL are suggested for further study.

In the general discussion chapter additional aspects of the experimental design, the distribution of the QTL effects, of the phenomena of epistasis and the subsequently and finally the use of the marked QTL in marker assisted breeding schemes are considered. In particular, it is highlighted how massive and genomewide SNP-marker data have entered livestock genomics and their used for mapping QTL and selection is described. Additionally, the importance of epistasis is discussed and the attempts to expand the statistical model towards accounting epistasis were described. The thesis ends with two appendixes, which contain the entropy-based information content of the data to map QTL and further QTL results not included in the three main chapters of the thesis, respectively.

ZUSAMMENFASSUNG

Die Kartierung von chromosomalen Bereichen mit einem Einfluss auf die Varianz eines quantitativen Merkmals (quantitaitve trait loci / QTL) hat im Bereich der Nutztierhaltung im Laufe der letzten Jahrzehnte erheblich an Bedeutung gewonnen. Das Wissen über die Position, den Erbgang und die Größe der QTL-Effekte führt zu einem besseren Verständnis der genetischen Architektur quantitativer Merkmale. Darüber hinaus werden die kartierten QTL in so genannten markergestützten Selektionsprogrammen eingesetzt. Vor Beginn des Genomik-Zeitalters wurden Mikrosatelliten als genetische Marker zur Kartierung der QTL genutzt.

Zur Kartierung von QTL bei Schweinen wurden häufig F_2-Kreuzungen erstellt. Diese entstanden aus genetisch divergent selektierten Elternlinien. Üblicherweise war die Zahl der F_2-Nachkommen nicht sehr hoch und lag bei etwa 300 Individuen. Diese Anzahl an Nachkommen ist zu gering um statistisch genügen Aussagekraft zu haben um QTL genau zu kartieren.

An der Universität Hohenheim wurde in den 90er Jahren ein großes F_2-Kreuzungsexperiment gestartet. Hierbei wurden drei F_2-Kreuzungen aus drei genetisch verschiedenen Elternlinien (Meishan, Pietrain und europäisches Wildschwein) gezüchtet. Die Nachkommenzahl lag bei rund 1000 Tieren. Diese wurden für etwa 50 Merkmale phänotypisiert. In früheren Studien wurden diese Kreuzungen separat ausgewertet und komplexere erbliche Zusammenhänge wurden hierbei außer acht gelassen. Verschiedene Forschergruppen zeigten, dass die Auswertung verschiedener QTL Experimente in einer gemeinsamen Analyse die statistische Aussagekraft deutlich erhöht. Zudem wurde gezeigt, dass der Erbgang der QTL häufig nicht rein additiv ist.

Ziel dieser Arbeit war die gemeinsame Analyse dieser drei F_2-Kreuzungen mit einer für den datensatz zugeschnittenen Methode, welche auch komplexere erbgänge der QTL berücksichtigt..

Im ersten Kapitel dieser Arbeit wurde ein Modell für die gemeinsame Analyse der drei Kreuzungen entwickelt. Das angewandte Modle stammt aus dem Bereich der Pflanzenzüchtung und wurde um Imprintingeffekte erweitert. Im ersten Schritt wurde für jedes Allel, kommend von einer der Elternlinie, ein additiver QTL-Effekt und für jede Kombination der elterlichen Allele ein dominanter QTL-Effekt geschätzt. Es wurden multiple QTL, multiple QTL-Allele und Imprinting-Effekte berücksichtigt. Das Model wurde mit

einem in der QTL-Analyse häufig für F_2-Kreuzungen benutzten Standardmodell vergliche, bei dem jede der dreiKreuzungen separat ausgewertet wird. Dabei wurden die folgenden Merkmale berücksichtigt: tägliche Zunahmen, Rückenspeckdicke und Schlachtkörpergewicht. Für das Merkmal tägliche Zunahme wurden 13, für Rückenspeckdicke 15 und für Schlachtkörpergewicht 16 QTL gefunden. Außerdem zeigten sich drei Imprinting-Effekte für tägliche Zunahme, vier bei Rückenspeckdicke und fünf bei Schlachtkörpergewicht. Es kann festgehalten werden, dass die Anzahl an gefundenen QTL in einer gemeinsamen Analyse deutlich höher war als bei separater Analyse der drei Designs. Des Weiteren war der Plot der Teststatistik über alle Chromosomen hinweg deutlich schärfer abgegrenzt, was zu schmaleren Konfidenzintervallen führte. In einigen Fällen wurden drei QTL-Allele entdeckt. Die statistische Aussagekraft ist auf Grund der reduzierten Anzahl an Parametern und aufgrund der Vielzahl an Nachkommen sehr hoch.

Im zweiten Kapitel der vorliegenden Arbeit wurde das in Kapitel eins entwickelte Modell bei Fettmerkmalen angewandt. Diese Merkmale stammen aus demselben F_2-Kreuzungsdesign, wie die im ersten Teil der Arbeit untersuchten Merkmale. Bei der Untersuchung von QTL werden Fettmerkmale standardmäßig mit untersucht. In der Vergangenheit wurden bereits eine Vielzahl von QTL-Studien zur Untersuchung von Fettmerkmalen durchgeführt und viele QTL entdeckt. Allerdings wurden in aller Regel klassische Fettmerkmale untersucht, wie zum Beispiel Rückenspeckdicke oder intramuskulärer Fettgehalt. Diese Merkmale können als Endprodukte einer Kaskade gesehen werden, welche durch verschiedene Genprodukte kontrolliert werden. Zur Interpretation der QTL Ergebnissen und zur Identifikation von Genen und Stoffwechselvorgängen, welche sich hinter den QTL verbergen, wäre es von Vorteil, direktere Merkmale zu untersuchen. Auf Grund dessen wurde in diesem Kapitel neben klassischen Merkmalen metabolische, zytologische und enzymatische Merkmale untersucht, welche eng in Zusammenhang mit den Endproduktmerkmalen stehen. Die untersuchten Merkmale waren die durchschnittliche Rückenspeckdicke und die Fettfläche als klassische Merkmale, die Anzahl an Zellen mit unterschiedlicher Größe als cytologische Merkmale, der lösliche Proteingehalt als metabolisches Merkmal und die NADH-Malatdehydrogenaseaktivität als Messgröße der Enzymaktivität. Die Auswertungen zeigten signifikante QTL auf den Chromosomen 1, 2, 4, 5, 6, 7, 8, 9, 14, 17 und 18. Bei dem Vergleich der QTL für die Merkmale zeigten sich einige überlappende Konfidenzintervalle, welche zudem in vielen Fällen sehr klein waren. Dies ist auf die hohen statistische Aussagekraft des Designs zurück zu führen. Bei der Analyse der Merkmale wurden einige

signifikante Imprinting-QTL gefunden. Auf Grund der kleinen und häufig überlappenden Konfidenzintervalle sowohl bei den klassischen Merkmalen, wie auch bei den zytologischen, enzymatischen und matabolischen Merkmalen war eine Kandidatengensuche für manche QTL möglich und wurde vorgenommen.

In der Schweinezucht, vor allem in der Zucht der Eberlinien, werden Muskel- und Wachstumsmerkmale standardmäßig miteinbezogen. Im dritten Kapitel wurde daher das entwickelte Model zur Auswertung von Muskel- und Wachstumsmerkmalen verwendet. Die Merkmale stammen, wie in Kapitel eins und zwei, aus den Kreuzungsversuchen der Universität Hohenheim. Die untersuchten Merkmale waren: Geburtsgewicht, Gewicht am Tag 21 und Tag 35, Schlachtgewicht lebend, Schlachtkörperlänge, Futterverwertung, Schinkengewicht, Gewicht der Schulterfleischs, Lendengewicht. und die Fleischfläche. Bei der Untersuchung der Merkmale wurde eine Vielzahl an QTL auf den Autosomen dieser Merkmale gefunden. Die meisten QTL befinden sich auf den Chromosomen 1, 2, 3, 4, 6 und 8. Auf den Chromosomen 9, 11, 13, 15, 17 und 18 wurden keine QTL gefunden. In den meisten Fällen waren die Konfidenzintervalle, wie auch in den anderen beiden Kapiteln, sehr klein. QTL mit einer extrem hohen Teststatistik wurden für das Merkmal Schlachtkörperlänge auf Chromosom 1, 4, und 17 gefunden. Der Variationskoeffizient für dieses Merkmal war extrem klein, was darauf zurück zu führen sein könnte, dass das Merkmal nur von wenigen Genen mit großen Effekten beeinflusst wird. Für die gefundenen QTL wurden Kandidatengene gesucht welche in weiteren Studien untersucht werden sollten.

Im letzten Kapitel, der allgemeinen Diskussion, werden zusätzliche Aspekte des Versuchsdesigns, der Verteilung der QTL_Effekte, des Phänomen der Epistasie und nicht zu letzt der verwendeten Marker diskutiert. Speziell die Entwicklung von genomweiten SNP-Markern und ihr Einsatz in der QTL-Analyse werden beschrieben. Außerdem wird die Bedeutung der Epistasie diskutiert und beschrieben wie das Model entsprechend erweitert werden könnte. Die Arbeit endet mit zwei Anhängen. Im ersten Anhang wird die Informationsgehaltberechung beschrieben. Der zweite Anhang beinhaltet weitere QTL-Ergebnisse welche nicht in einem der drei Kapitel diskutiert wurden.

APPENDIX 1

In the statistical approach it is assumed that two founder breeds, i and j, of an F_2-cross are alternative homozygous at a QTL, i.e. that are Q_iQ_i and Q_jQ_j. Taking the parental origin into account, four genotypes are present in the F_2-population, i.e. $Q_i^pQ_i^m$, $Q_i^pQ_j^m$, $Q_j^pQ_i^m$ and $Q_j^pQ_j^m$. The upper subscript denotes for the parental origin, either paternal (p) or maternal (m) inherited. The ability to map additive (imprinting) QTL depends also an the ability to distinguish between $Q_i^pQ_i^m$ and $Q_j^pQ_j^m$ ($Q_i^pQ_j^m$ and $Q_j^pQ_i^m$) genotypes in the F_2-generation. Naturally, these genotypes are not observable directly, but probabilities are estimated using molecular markers. For a visualisation of the information content to distinguish the above mentioned genotypes and hence to map additive and imprinting QTL effects the contribution to the entropy were calculated, following Kruglyak et al (1996) and especially Mantey et al. (2005).

For additive effects, the entropy of an F_2-individual k was calculated as

$$E_k = -p_1 \log_2(p_1) - p_2 \log_2(p_2), \text{ with}$$

$$p_1 = \frac{pr(Q_i^pQ_i^m)}{pr(Q_i^pQ_i^m) + pr(Q_j^pQ_j^m)} \text{ and } p_2 = \frac{pr(Q_j^pQ_j^m)}{pr(Q_i^pQ_i^m) + pr(Q_j^pQ_j^m)} = 1 - p_1,$$

where $pr(Q_i^pQ_i^m) + pr(Q_j^pQ_j^m)$ is also denoted as p_k. The information content for the additive effect (IC_A) is calculated as

$$IC_A = 1 - \frac{\sum_{k=1}^{n} p_k E_k}{\sum_{k=1}^{n} p_k}, \text{ where } n \text{ is the number of } F_2\text{-individuals.}$$

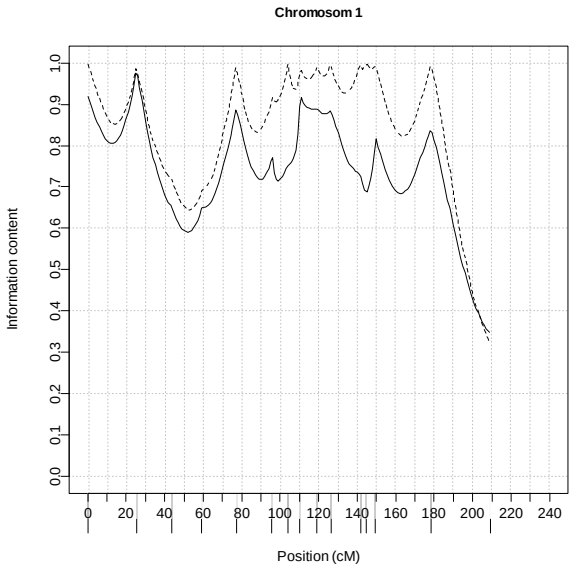
For the calculation of imprinting information content (IC_I), p_1 and p_2 are defined as

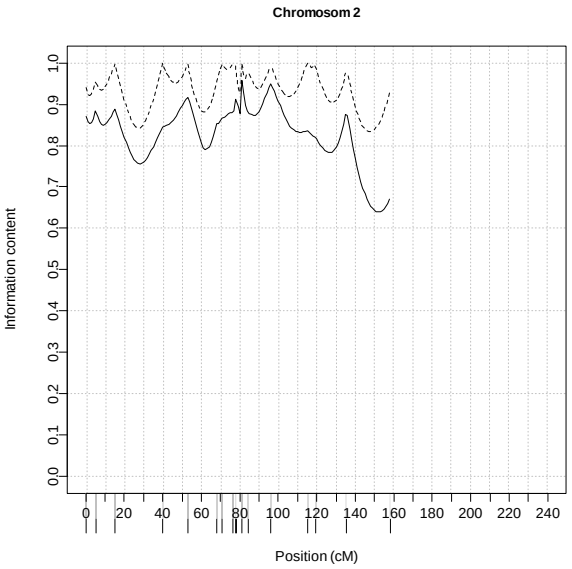
$$p_1 = \frac{pr(Q_i^pQ_j^m)}{pr(Q_i^pQ_j^m) + pr(Q_j^pQ_i^m)} \text{ and } p_2 = \frac{pr(Q_j^pQ_i^m)}{pr(Q_i^pQ_j^m) + pr(Q_j^pQ_i^m)} = 1 - p_1 ,$$

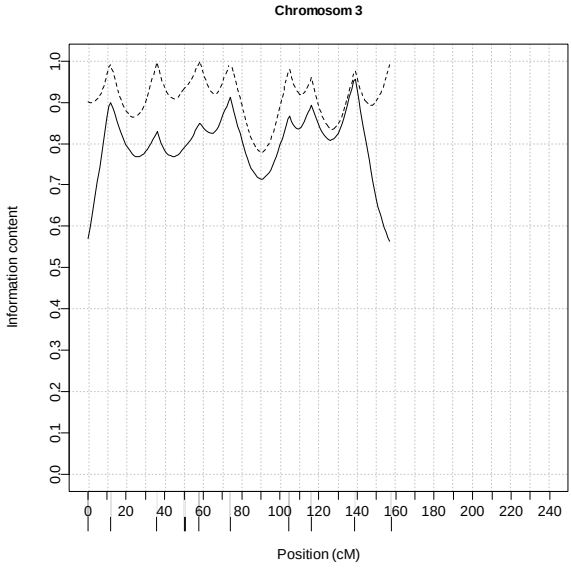
where $pr(Q_i^pQ_j^m) + pr(Q_j^pQ_i^m)$ is denoted as p_k. Subsequently, the imprinting information content was

$$IC_I = 1 - \frac{\sum_{k=1}^{n} p_k E_k}{\sum_{k=1}^{n} p_k}.$$

The information content were calculated for every cM along the autosomes. In the following figures they are presented.


Chromosom 1
Information content
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 2
Information content
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 3
Information content
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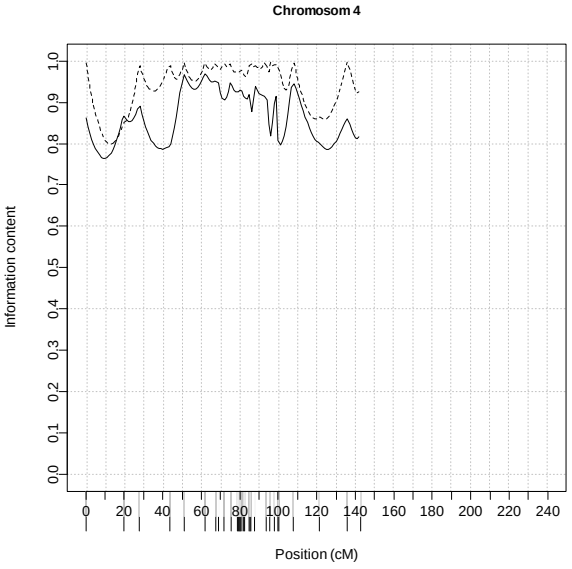
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 4
Information content
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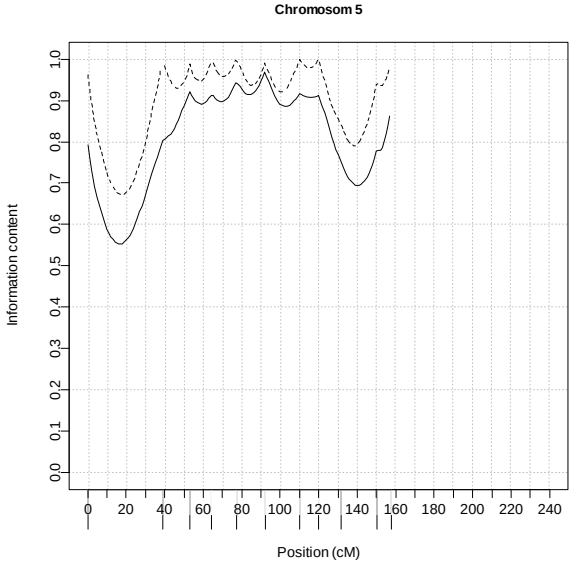
Position (cM)


Chromosom 5
Information content
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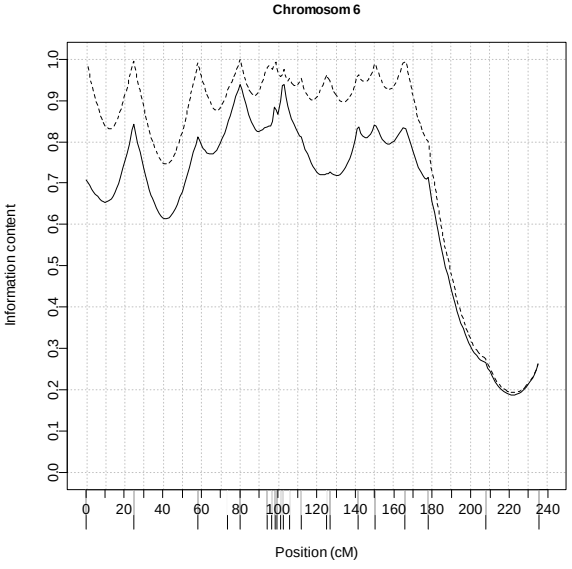
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 6
Information content
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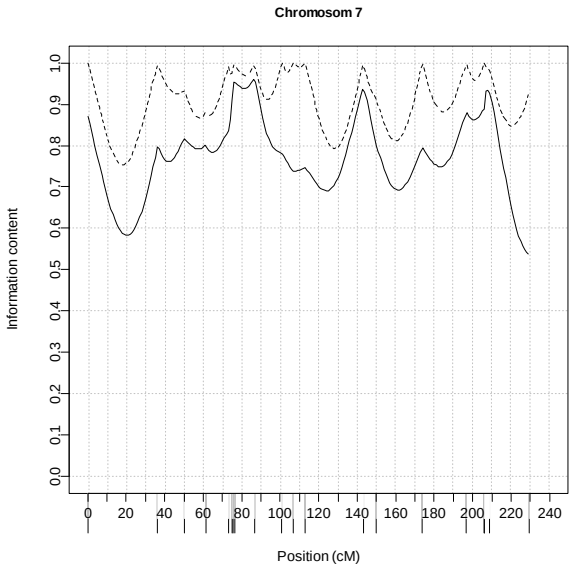
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 7
Information content
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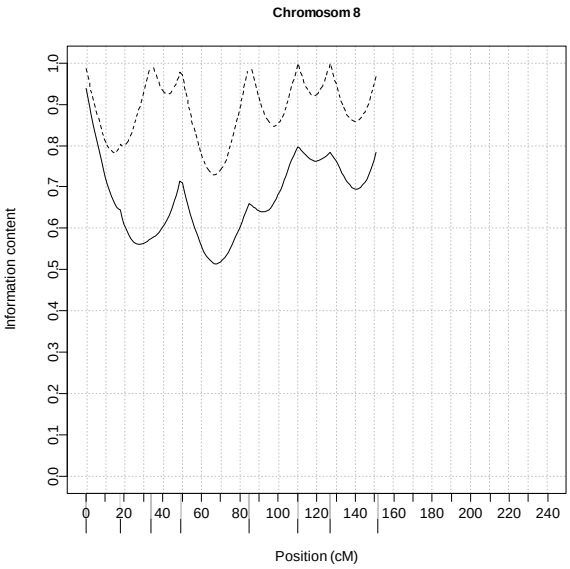
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 8
Information content
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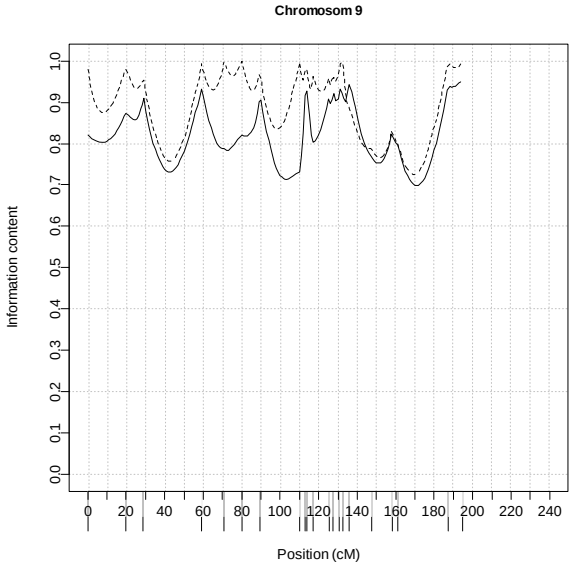
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 9
Information content
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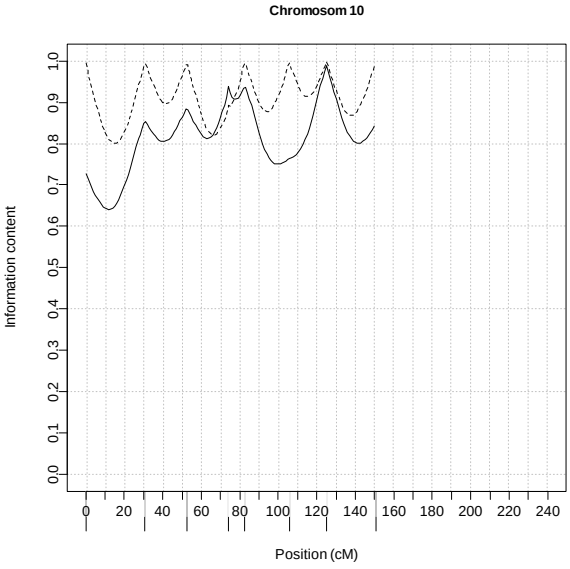
Position (cM)


Chromosom 10
Information content
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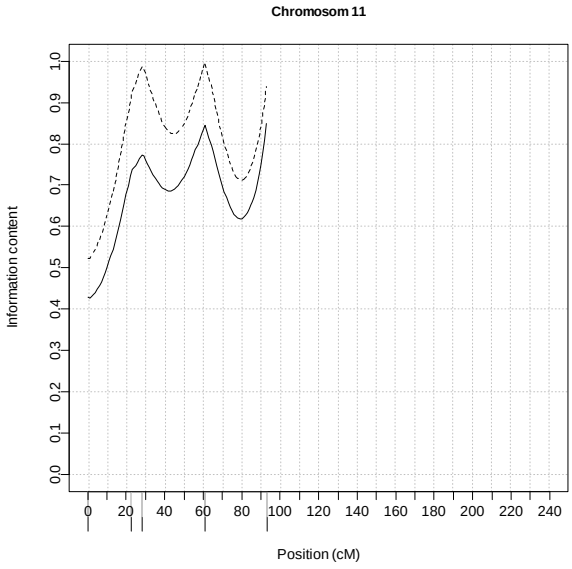
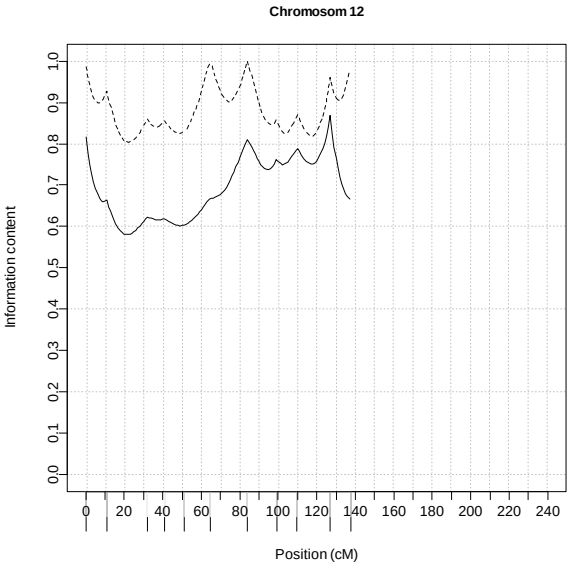
Position (cM)


Chromosom 11
Information content
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 12
Information content
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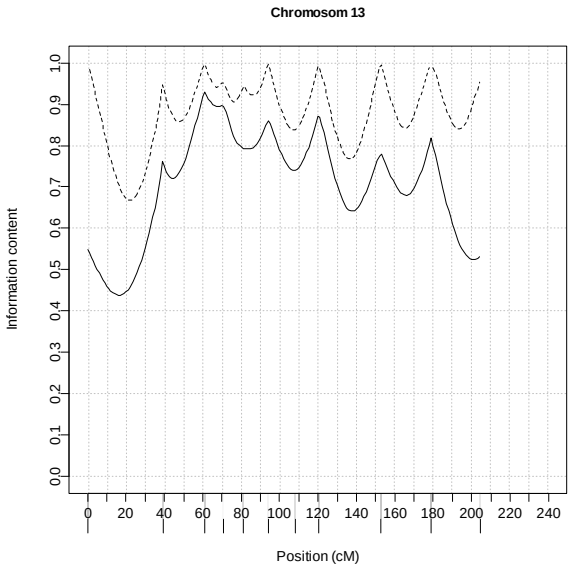
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 13
Information content
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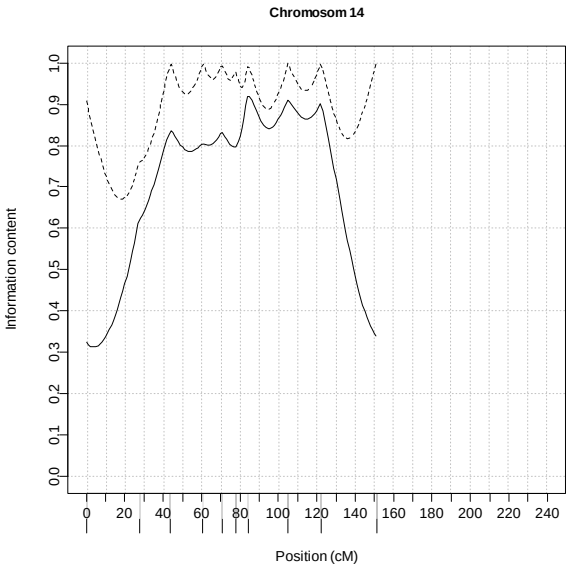
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 14
Information content
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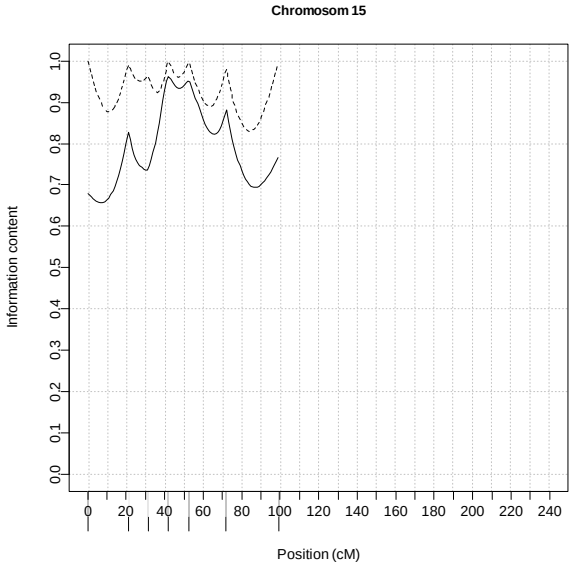
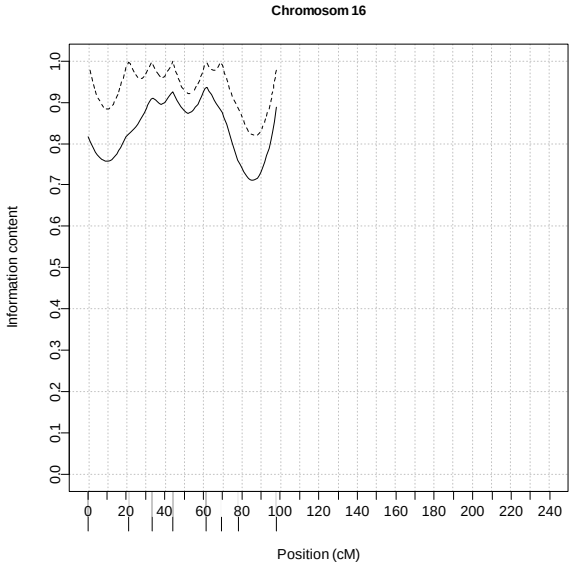
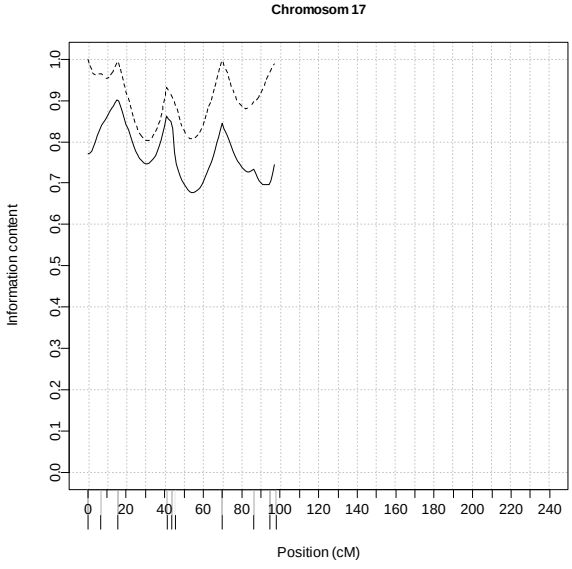
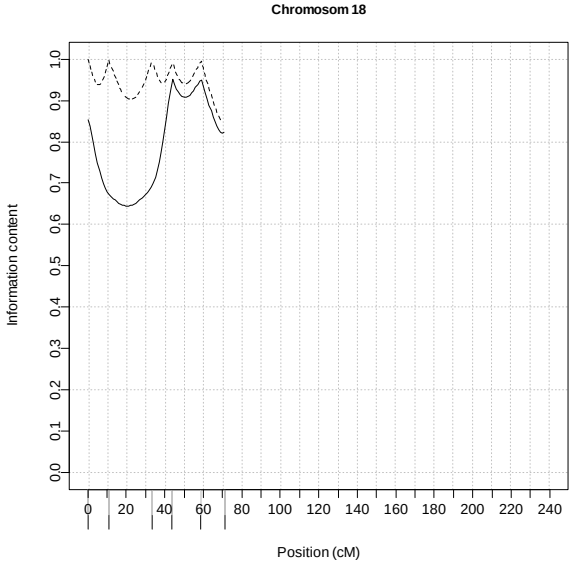
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 15
Information content
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 16
Information content
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 17
Information content
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)


Chromosom 18
Information content
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0 20 40 60 80 100 120 140 160 180 200 220 240
Position (cM)

Figures 1-18: Information content for additive (dashed line) and imprinting (soild line) effects for every chromosome in the joint design. Marker positions are indicated as bars under the cM description on the x-axis. The marker map can be found in Rückert and Bennewitz (2010).

References:

Kruglyak L., Daly MJ., Reeve-Daly MP. and Lander ES. 1996. Parametric and Nonparametric Linkage Analysis: A Unified Multipoint Approach. Am. J. Hum. Genet. 58:1347-1363.

Mantey C., Brockmann GA., Kalm E. and Reinsch N. 2005. Mapping and exclusion mapping of genomic imprinting effects in mouse F_2 families. J. Heredity 96:329-338.

Rückert C. and Bennewitz J. 2010. Joint analysis of three connected F_2-crosses on pigs. Genet. Sel. Evol. 42:40.

APPENDIX 2

In addition to the traits included in the previous chapters, a number of additional traits were recorded for most of the F2-animals of the design.
For trait definition and abbreviation see Table 1.
A summary statistic is given in Table 2. The traits were analysed with the multi-allelic-multi-QTL-model applied in the previous chapters.
The results are shown in the Table 3.

The results are not discussed in detail, but it can be observed that number of mapped QTL is in general high compared with the results of the previous analysis conducted by Geldermann et al. (2003; J. Anim. Breed. Genet. 120:363–393). This underlines the high statistical power of the applied approach.

Table 1: Trait definition and abbreviations

Definition of traits	Abbr.
Food consumption between 110-210 days of live	FoodC
Abdominal fat weight	Flomen
Ham external fat weight	HFW
Sholder external fat weight	SFW
Back fat weight	BFW
Fat content	FC
Sholder fat depth	SFD
Fat depth at 10th rib	RFD
Loin fat depth	LFD
Ham weight including bones and external fat	HWBF
Lean cuts	LC
Weight of ham meat relativ to half carcass	R1
Weight of ham relative to half carcass	R2
Weight of heart	Heart
Weight of liver	Liver
Numbers of teats (both sides)	Teats
Usability of carcass	CU
Weight of head	Head
Fat to meat ratio at 13th/14 th rib	FMR
Meat area in relation to area of meat	R3

Table 2: Number of observations (n), mean, standard deviation (Sd), minimum (Min) and maximum (Max) of the phenotypic observations and coefficient of variation (CV)

Trait	Cross	n	Mean	Sd	Min	Max	CV
FoodC	MxP	316	221,94	41,05	87,80	307,50	18,49
[kg]	WxP	315	178,77	34,43	79,70	259,60	19,26
	WxM	335	194,18	35,62	87,80	290,00	18,34
	Joint	966	198,23	41,09	79,70	307,50	20,73
Flomen	MxP	316	0,86	0,41	0,10	2,75	47,59
[kg]	WxP	315	0,50	0,25	0,00	1,30	51,12
	WxM	335	0,93	0,38	0,05	2,35	41,27
	Joint	966	0,77	0,40	0,00	2,75	52,61
HFW	MxP	316	2,60	0,82	0,45	5,15	31,47
[kg]	WxP	315	1,42	0,49	0,35	2,95	34,46
	WxM	335	2,26	0,66	0,35	4,00	29,24
	Joint	966	2,10	0,83	0,35	5,15	39,56
SFW	MxP	316	1,26	0,36	0,20	2,35	28,13
[kg]	WxP	315	0,74	0,23	0,20	1,50	31,59
	WxM	335	1,03	0,29	0,20	1,90	28,64
	Joint	966	1,01	0,37	0,20	2,35	36,31
BFW	MxP	316	2,41	0,91	0,20	5,25	37,74
[kg]	WxP	315	1,54	0,65	0,20	3,85	42,46
	WxM	335	2,27	0,78	0,30	4,45	34,47
	Joint	966	2,08	0,87	0,20	5,25	42,09
FC	MxP	316	18,33	3,78	8,31	27,97	20,61
[%]	WxP	315	14,21	3,00	6,79	22,73	21,12
	WxM	335	23,22	3,42	12,04	31,36	14,74
	Joint	966	18,68	5,04	6,79	31,36	26,95
SFD	MxP	316	36,82	7,67	12,00	58,00	20,83
[mm]	WxP	315	30,26	5,92	14,00	52,00	19,58
	WxM	335	39,83	7,88	11,00	63,00	19,78
	Joint	966	35,72	8,25	11,00	63,00	23,10
RFD	MxP	316	23,40	6,21	7,00	39,00	26,54
[mm]	WxP	315	20,06	4,82	8,00	34,00	24,02
	WxM	335	26,79	6,52	7,00	46,00	24,33
	Joint	966	23,49	6,52	7,00	46,00	27,75
LFD	MxP	316	23,57	7,78	7,00	54,00	33,01
[mm]	WxP	315	18,17	5,62	7,00	36,00	30,95
	WxM	335	28,83	7,15	7,00	49,00	24,81
	Joint	966	23,63	8,18	7,00	54,00	34,61
HWBF	MxP	316	10,43	1,85	2,70	15,10	17,75
[kg]	WxP	315	8,53	1,74	3,20	13,05	20,39
	WxM	335	7,28	1,45	2,05	10,95	19,91
	Joint	966	8,72	2,13	2,05	15,10	24,38

LC	MxP	316	45,40	4,20	35,79	58,30	9,24
[%]	WxP	315	53,63	3,62	44,94	62,79	6,75
	WxM	335	39,42	3,56	30,40	51,60	9,02
	Joint	966	46,01	6,97	30,40	62,79	15,14
R1	MxP	316	18,74	2,18	13,18	25,97	11,62
[%]	WxP	315	22,95	1,91	18,83	28,51	8,31
	WxM	335	16,44	1,63	12,54	21,98	9,91
	Joint	966	19,31	3,31	12,54	28,51	17,13
R2	MxP	316	41,20	1,61	35,82	46,10	3,92
[%]	WxP	315	42,77	1,29	37,99	46,54	3,01
	WxM	335	41,68	1,25	35,76	45,67	2,99
	Joint	966	41,88	1,53	35,76	46,54	3,66
Heart	MxP	316	287,19	49,53	183,00	484,00	17,25
[g]	WxP	315	234,07	41,16	120,00	406,00	17,59
	WxM	335	210,30	33,15	83,00	314,00	15,76
	Joint	966	243,21	52,62	83,00	484,00	21,64
Liver	MxP	316	1353,03	223,97	602,00	2075,00	16,55
[g]	WxP	315	1218,74	205,45	650,00	1867,00	16,86
	WxM	335	1169,50	191,00	527,00	1928,00	16,33
	Joint	966	1245,59	220,82	527,00	2075,00	17,73
Teats	MxP	316	14,27	1,22	11,00	18,00	8,53
[counted]	WxP	315	11,71	1,36	8,00	16,00	11,58
	WxM	335	13,68	1,29	11,00	18,00	9,41
	Joint	966	13,23	1,68	8,00	18,00	12,73
CU	MxP	316	80,23	2,04	73,10	89,60	2,54
[%]	WxP	314	80,28	2,67	70,00	89,10	3,33
	WxM	335	78,03	2,61	58,70	84,60	3,34
	Joint	965	79,48	2,67	58,70	89,60	3,37
Head	MxP	316	4,84	0,85	2,02	7,30	17,54
[kg]	WxP	315	3,59	0,57	1,85	5,07	15,81
	WxM	335	3,86	0,73	1,65	6,25	18,84
	Joint	966	4,09	0,90	1,65	7,30	21,94
FMR	MxP	316	0,72	0,22	0,28	1,39	29,93
[%]	WxP	313	0,51	0,15	0,19	1,08	29,14
	WxM	335	1,27	0,35	0,52	2,62	27,63
	Joint	964	0,85	0,41	0,19	2,62	48,63
R3	MxP	316	0,59	0,07	0,42	0,78	12,27
[cm^2/cm^2]	WxP	313	0,67	0,06	0,48	0,84	9,51
	WxM	335	0,45	0,07	0,28	0,66	15,70
	Joint	964	0,57	0,11	0,28	0,84	20,02

Table 3: Results of all traits measured and analysed.

Trait	SSC	Pos	CI [a]	*F*-value	p_{add} [b]	p_{dom} [c]	p_{imp} [d]	Mode[e]	Order of effects[f]
FoodC	1	90	[77.3; 104.1] [SW2130; IGFR]	6.60	<0.0001	0.9751	0.1331	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	2	76	[70.6; 78.3] [MYOD1; INSR]	3.88	<0.0001	0.1403	0.3718	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	4	95	[81.0; 107.7] [SDHC; SW2435]	3.55	0.0001	0.1684	0.8568	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	5	80	[53.0; 110.0] [SW2425; IGF1]	3.90	0.0003	0.2273	0.0785	(- -)	$\hat{a}_P > \hat{a}_W > \hat{a}_M$
	6	100	[96.4; 101.2] [RYR; A1BG]	3.41	0.0195	0.0505	0.0245	(pat)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	8	11	[0.0; 34.0] [SW905; SW933]	4.08	0.0120	0.0687	0.0066	(mat)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	16	0	[0.0; 21.2] [S0111; SW1035]	3.73	0.6925	0.0165	0.0017	(mat)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	17	80	[69.9; 94.6] [SJ063; EEF1A2]	3.01	0.0031	0.7670	0.0252	(mat)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
Flomen	1	123	[104.1; 178.5] [IGFR; SW705]	4.26	<0.0001	0.1791	0.3112	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	2	76	[70.6; 78.3] [MYOD1; INSR]	3.13	0.0001	0.3513	0.6821	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	6	103	[96.4; 106.0] [RYR; SKI]	7.39	<0.0001	0.0005	0.0083	(pat)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	7	75	[61.3; 86.5] [ID4ECO; S0102]	5.53	<0.0001	0.1749	0.2222	(- -)	$\hat{a}_P > \hat{a}_W > \hat{a}_M$
	9	194	[187.4; 194.6] [EAE; SW1349]	3.19	0.0153	0.0049	0.8714	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
HFW	1	93	[77.3; 104.1] [SW2130; IGFR]	9.98	<0.0001	0.4929	0.0035	(nc)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	2	9	[0.0; 14.9] [SW2443; SW2623]	2.91	0.0291	0.9272	0.0018	(mat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	2	76	[70.6; 78.3] [MYOD1; INSR]	5.48	<0.0001	0.0234	0.8933	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	6	100	[96.4; 101.2] [RYR; A1BG]	6.04	<0.0001	0.0013	0.2101	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	9	194	[187.4; 194.6] [EAE; SW1349]	3.39	0.0557	0.0011	0.9567	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	16	21	[0.0; 33.3] [S0111; SW419]	3.11	0.0289	0.0276	0.0608	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	17	55	[45.4; 69.9] [RNPC2; SJ063]	2.43	0.0054	0.9123	0.0998	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
SFW	1	100	[77.3; 119.2] [SW2130; S0082]	5.83	<0.0001	0.2638	0.0237	(nc)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	1	194	[178.5; 209.1] [SW705; EAA]	2.87	0.0008	0.0887	0.7860	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	2	0	[0.0; 5.2] [SW2443; SWC9]	2.74	0.0006	0.7934	0.1361	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	2	76	[70.6; 81.0] [MYOD1; SW395]	4.86	<0.0001	0.0085	0.9763	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	3	18	[0.0; 35.9] [SERPINE1; S0206]	3.24	0.0186	0.0083	0.1280	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	5	157	[150.4; 157.9] [MYF5; SW967]	4.21	0.4347	0.3623	<0.0001	(nc)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	6	100	[96.4; 101.2] [RYR; A1BG]	5.76	<0.0001	0.0472	0.0053	(pat)	$\hat{a}_M > \hat{a}_W > \hat{a}_P$
	7	30	[0.0; 50.0] [S0025; SWR1078]	4.90	<0.0001	0.0739	0.1639	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	7	62	[50.0; 73.3] [SWR1078; CYPA]	2.45	0.0077	0.2514	0.1560	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$

BFW	1	90	[77.3; [[SW2130;	104.1] IGFR]	4.33	0.0009	0.4398	0.0055	(mat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	1	145	[126.3; [SW780;	149.6] TGFBR1]	8.09	<0.0001	0.0077	0.2355	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	2	77	[70.6; [MYOD1;	81.0] SW395]	6.35	<0.0001	0.0232	0.9164	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	6	100	[96.4; [RYR;	101.2] A1BG]	4.81	<0.0001	0.0512	0.0833	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	17	91	[69.9; [SJ063;	97.9] SW2427]	3.36	0.0051	0.5162	0.0068	(mat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
FC	1	146	[126.3; [SW780;	178.5] SW705]	6.38	<0.0001	0.0485	0.6029	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	2	14	[5.2; [SWC9;	39.9] S0141]	7.27	<0.0001	0.5711	<0.0001	(mat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	2	77	[52.9; [SW240;	81.0] SW395]	4.68	<0.0001	0.1276	0.7562	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	4	66	[50.9; [SW2128;	75.3] S0073]	3.61	<0.0001	0.4217	0.3007	(- -)	$\hat{a}_W > \hat{a}_M = \hat{a}_P$
	4	101	[99.6; [NGFB;	107.7] SW2435]	4.20	0.0437	0.0050	0.0152	(nc)	$\hat{a}_W > \hat{a}_M = \hat{a}_P$
	6	100	[96.4; [RYR;	101.2] A1BG]	11.66	<0.0001	0.0035	0.0223	(nc)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	7	82	[61.3; [ID4ECO;	100.9] PSMA4]	3.27	0.0004	0.1126	0.7379	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	11	85	[61.0; [SW435;	93.3] SW1827]	3.30	0.5520	0.0068	0.0054	(nc)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	12	53	[40.7; [GH1-H;	64.5] SW874]	2.25	0.0667	0.0123	0.8867	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	18	33	[10.9; [EAI;	43.6] SW787]	3.07	0.0005	0.1454	0.9667	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
SFD	1	131	[119.2; [S0082;	141.7] SW803]	5.06	<0.0001	0.7218	0.3505	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	2	0	[0.0; [SW2443;	39.9] S0141]	3.58	0.0340	0.9451	0.0001	(mat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	2	76	[39.9; [S0141;	81.0] SW385]	4.56	<0.0001	0.2788	0.1533	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	6	100	[96.4; [RYR;	106.0] SKI]	5.97	0.0003	0.0079	0.0034	(pat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	7	75	[61.3; [ID4ECO	86.5] S0102]	3.51	0.0002	0.0884	0.5632	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
RFD	1	118	[110.3; [SW307;	126.3] SW780]	5.87	<0.0001	0.4932	0.5667	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	1	169	[149.6; [TGFBR1;	209.1] EAA]	3.03	0.0004	0.3400	0.5010	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	2	4	[0.0; [SW2443;	14.9] SW2623]	4.85	0.0008	0.9372	<0.0001	(mat)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	2	68	[52.9; [SW240;	81.0] SW395]	4.32	<0.0001	0.8984	0.2717	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	6	100	[96.4; [RYT;	101.2] A1BG]	5.86	0.0046	0.0009	0.0028	(pat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	7	61	[50.0; [SWR1078;	73.3] CYPA]	3.44	0.0008	0.5694	0.0151	(pat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	7	75	[61.3; [ID4ECO;	76.2] TNFB]	11.80	<0.0001	0.3360	0.0507	(- -)	$\hat{a}_W > \hat{a}_P > \hat{a}_M$
	9	194	[187.6; [EAE;	194.6] SW1349]	2.98	0.0661	0.0036	0.3683	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
LFD	1	162	[149.6; [TGFBR1;	178.5] SW705]	3.20	0.0001	0.4173	0.4642	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	2	10	[0.0; [SW2443;	39.9] S0141]	4.45	0.1010	0.6938	<0.0001	(mat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$

	2	76	[70.6; [MYOD1;	81.0] SW395]	2.99	0.0007	0.1090	0.8058	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	6	95	[80.0; [S0087;	98.3] LIPE]	6.48	0.0019	0.0023	0.0005	(pat)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	7	75	[61.3; [ID4ECO;	76.2] TNFB]	7.31	<0.0001	0.2008	0.0366	(nc)	$\hat{a}_P > \hat{a}_W > \hat{a}_M$
	11	52	[28.4; [SW1632;	61.0] SW435]	3.14	0.6195	0.0245	0.0054	(pat)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
HWBF	1	88	[77.3; [SW2130;	104.1] IGFR]	7.53	<0.0001	0.9127	0.0222	(nc)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	2	76	[70.6; [MYOD1;	78.3] INSR]	3.94	0.0006	0.0142	0.3802	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	3	0	[0.0; [SERPINE;	11.6] SW72]	3.83	<0.0001	0.2903	0.2789	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	4	72	[62.1; [S0145;	80.1] MPZ]	5.71	<0.0001	0.3059	0.6338	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	5	120	[110.0; [IGF1;	150.4] MYF5]	4.18	0.0015	0.9309	0.0005	(mat)	$\hat{a}_W > \hat{a}_M = \hat{a}_P$
	6	86	[73.7; [FTO;	94.4] ETH5001]	4.46	<0.0001	0.0154	0.2311	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	7	67	[50.0; [SWR1078,	75.2] KE6]	4.00	<0.0001	0.4828	0.0922	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	8	14	[0.0; [SW905;	34.0] SW933]	5.92	<0.0001	0.2010	0.1047	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	10	63	[30.6; [SW443;	74.1] GAS1]	4.04	0.3092	0.0062	0.0023	(mat)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	14	56	[43.8; [SW2038;	60.7] SW540]	1.35	0.9661	0.0317	0.6929	(- -)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	14	91	[60.7; [SW540;	105.1] SW2488]	4.01	<0.0001	0.9639	0.8628	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	16	0	[0.0; [S0111;	21.2] SW1035]	2.37	0.0834	0.3706	0.0352	(mat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
LC	1	107	[77.3; [SW2130;	119.2] S0082]	7.00	<0.0001	0.7438	0.0456	(mat)	$\hat{a}_W > \hat{a}_P > \hat{a}_M$
	1	170	[149.6; [TGFBR1;	209.1] EAA]	3.44	<0.0001	0.8516	0.1289	(- -)	$\hat{a}_W > \hat{a}_P > \hat{a}_M$
	2	23	[5.2; [SWC9;	39.9] S0141]	9.62	0.0002	0.7538	<0.0001	(nc)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	2	77	[70.6; [MYOD1;	81.0] SW395]	5.40	<0.0001	0.0425	0.8105	(- -)	$\hat{a}_W > \hat{a}_P > \hat{a}_M$
	4	67	[62.1; [SW1073;	69.1] VATP]	3.83	<0.0001	0.4012	0.0363	(mat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	4	101	[98.1; [TSHB;	107.7] SW2435]	3.82	0.0414	0.0668	0.0025	(nc)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	6	100	[96.4; [RYR;	101.2] A1BG]	14.73	<0.0001	0.0104	0.0689	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	12	0	[0.0; [S0143;	32.0] SW957]	2.64	0.0116	0.0863	0.3117	(- -)	$\hat{a}_W = \hat{a}_P > \hat{a}_M$
	16	53	[43.9; [S0077;	61.5] S0026]	3.49	0.0002	0.0630	0.7291	(- -)	$\hat{a}_W = \hat{a}_P > \hat{a}_M$
	17	78	[45.4; [RNPC;	97.9] SW2427]	3.50	0.0039	0.7450	0.0038	(mat)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	18	27	[10.9; [EAI;	43.6] SW787]	3.44	0.0009	0.0983	0.1216	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
R1	6	100	[96.4; [RYR;	101.2] A1BG]	13.17	<0.0001	0.0528	0.1574	(- -)	$\hat{a}_W > \hat{a}_M = \hat{a}_P$
R2	1	209	[178.5; [SW705;	209.1] EAA]	3.81	0.0004	0.1766	0.0108	(	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	6	69	[58.1; [SW1057;	80.0] S0087}	4.59	<0.0001	0.2136	0.9448	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	13	70	[39.2;	94.2]	5.35	0.0029	0.0020	0.0122	(mat)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$

	17	44	[S0076; 69.9] [15.6; SJ063] [S0296; S0068]	5.00	0.0003	0.1761	0.0010	(mat)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
Heart	1	166	[149.6; 209.1] [TGFBR1; EAA]	3.91	0.0018	0.4495	0.0032	(pat)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	2	5	[0.0; 14.9] [SW2443; SW2623]	10.01	<0.0001	0.4373	<0.0001	(mat)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	2	77	[76.5; 78.3] [MEF2B; INSR]	3.27	0.0250	0.4224	0.0071	(mat)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	4	71	[62.1; 75.3] [SW1073; S0073]	5.25	<0.0001	0.1318	0.4756	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	5	120	[110.0; 150.4] [IGF1; MYF5]	4.28	0.5662	0.0313	<0.0001	(mat)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	6	84	[24.8; 101.2] [SW1329; A1BG]	3.80	0.1708	0.2522	0.0001	(mat)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	7	81	[73.3; 100.9] [CYPD; PSMA4]	6.33	<0.0001	0.1683	0.2196	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	8	11	[0.0; 34.0] [SW905; SW933]	3.58	0.0019	0.1385	0.0225	(nc)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	10	63	[30.6; 82.7] [SW443; SWR1849]	3.70	0.0019	0.4636	0.0059	(mat)	$\hat{a}_W > \hat{a}_M > \hat{a}_P$
	18	59	[43.6; 71.2] [SW787; GCK]	2.78	0.0633	0.0039	0.5198	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
Liver	1	145	[141.7; 149.6] [SW803; TGFBR1]	4.61	<0.0001	0.2446	0.7771	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	2	84	[81.0; 96.0] [SW395; S0010]	3.48	0.0009	0.0229	0.1543	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	4	69	[62.1; 80.1] [SW1073; MPZ]	3.34	<0.0001	0.4446	0.6072	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	5	64	[53.0; 77.3] SW2425; S0005]	2.70	0.0073	0.0690	0.5606	(- -)	$\hat{a}_W > \hat{a}_P > \hat{a}_M$
	5	120	[110.0; 150.4] [IGF1; MYF5]	5.36	<0.0001	0.8371	0.0011	(mat)	$\hat{a}_W > \hat{a}_M > \hat{a}_P$
	8	6	[0.0; 18.0] [SW905; PGCMUT]	4.89	<0.0001	0.2620	0.8572	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	10	30	[0.0; 52.5] [SW830; SW497]	3.23	0.1219	0.0177	0.0126	(mat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	16	0	[0.0; 21.2] [S0111; SW1035]	3.24	0.1017	0.0699	0.0086	(nc)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
Teats	1	168	[149.6; 178.5] [TGFBR1; SW705]	9.28	<0.0001	0.1182	0.4913	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	8	60	[34.0; 110.1] [SW933; SW16]	3.22	0.0063	0.0788	0.1643	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	10	118	[105.7; 150.8] [SW2000; SW2067]	6.58	<0.0001	0.2951	0.6877	(- -)	$\hat{a}_M > \hat{a}_P = \hat{a}_W$
	12	131	[109.8; 137.9] [S0106; SW605]	4.85	0.0007	0.4863	0.0032	(mat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	17	86	[69.9; 94.6] [SJ063; EEF1A2]	3.55	0.0030	0.0109	0.1231	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
CU	1	47	[25.4; 77.3] [SWR485; SW2130]	3.98	<0.0001	0.7093	0.4830	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	1	129	[110.3; 141.7] [SW307; SW803]	3.25	0.0003	0.4278	0.0967	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	6	102	[80.0; 106.0] [S0087; SKI]	4.34	0.0007	0.0033	0.2001	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	12	74	[64.5; 99.3] [SW874; S0147]	3.18	0.0208	0.0477	0.0183	(pat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
Head	1	87	[77.3; 95.8] [SW2130; EEF1A1]	10.20	<0.0001	0.6314	0.0688	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	2	83	[78.3; 96.0] [MEF2B; S0010]	4.64	0.0006	0.0004	0.5247	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$

	3	0	[0.0; 11.6] [SERPINE; SW72]	3.00	0.0003	0.2603	0.3356	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	3	56	[11.6; 74.0] [SW72; SW828]	3.65	0.0002	0.0491	0.5282	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	4	69	[62.1; 75.3] [SW1073; S0073]	9.57	<0.0001	0.3765	0.2451	(- -)	$\hat{a}_P > \hat{a}_M > \hat{a}_W$
	7	74	[61.3; 75.2] [ID4ECO; KE6]	17.89	<0.0001	0.4536	0.0269	(nc)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	8	8	[0.0; 18.0] [SW905; PGCMUT]	5.74	<0.0001	0.1810	0.1715	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
FMR	1	89	[59.3; 110.3] [SW2130; S0082]	3.14	0.0368	0.5459	0.0059	(mat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	1	146	[126.3; 178.5] [SW780; SW705]	5.90	<0.0001	0.4420	0.5810	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	1	189	[149.6; 209.1] [TGFBR1; EAA]	3.96	0.0001	0.2291	0.4170	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	2	22	[0.0; 39.9] [SW2443; S0141]	8.42	0.0007	0.8087	<0.0001	(mat)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	2	78	[52.9; 81.0] [SW240; SW395]	3.39	0.0002	0.2745	0.5516	(- -)	$\hat{a}_M > \hat{a}_P > \hat{a}_W$
	6	100	[96.4; 101.2] [RYR; A1BG]	8.61	<0.0001	0.0856	0.0083	(nc)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
	17	73	[45.4; 97.9] [RNPC2; SW2427]	2.67	0.0093	0.7572	0.0254	(mat)	$\hat{a}_M = \hat{a}_P = \hat{a}_W$
	18	27	[10.9; 43.6] [EAI; SW787]	3.34	0.0005	0.0901	0.3058	(- -)	$\hat{a}_M = \hat{a}_P > \hat{a}_W$
R3	1	170	[149.6; 209.1] [TGFBR1; EAA]	6.10	<0.0001	0.2528	0.7273	(- -)	$\hat{a}_P > \hat{a}_W > \hat{a}_M$
	2	12	[0.0; 39.9] [SW2443; S0141]	8.63	0.0004	0.3738	<0.0001	(nc)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	2	74	[52.9; 81.0] [SW240; SW395]	4.16	<0.0001	0.1426	0.4555	(- -)	$\hat{a}_P > \hat{a}_W > \hat{a}_M$
	6	10	[96.4; 101.2] [RYR; A1BG]	9.08	<0.0001	0.0720	0.0058	(nc)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	17	78	[45.4; 97.9] [RNPC2; SW2427]	3.13	0.0073	0.8477	0.0063	(mat)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$
	18	27	[10.9; 43.6] [EAI; SW787]	3.25	0.0015	0.0831	0.1759	(- -)	$\hat{a}_P > \hat{a}_M = \hat{a}_W$

[a] confidence interval (CI); [b] error probability for additive effects; [c] error probability for dominant effects; [d] error probability for imprinting effects; [e] Mode of imprinting ((--) imprinting not significant, (mat) maternal imprinting, (pat) paternal imprinting, (nc) not consistent)), [f] $\hat{a}_P$ estimated effect of Pietrain breed, $\hat{a}_M$ estimated effect of Meishan breed, $\hat{a}_W$ estimated effect of wild boar breed

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EIDESSTATTLICHE ERKLÄRUNG

Ich versichere an Eides Statt, dass ich die vorliegende Arbeit selbstständig verfasst habe. Alle statistischen Analysen, welche auch in den Vorabveröffentlichungen aufgeführt werden wurden von mir selbst durchgeführt. Alle Stellen, die wörtlich oder dem Sinn nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche kenntlich gemacht. Ich versichere außerdem, dass ich keine andere als die angegebene Literatur verwendet habe. Diese Versicherung bezieht sich auch auf alle in der Arbeit enthaltenen Zeichnungen, Skizzen, bildlichen Darstellungen und dergleichen.

Die Arbeit wurde bisher keiner anderen Prüfungsbehörde vorgelegt und auch noch nicht veröffentlicht.

Altenriet im Dezember 2011

Christine Rückert

DANKSAGUNG

An erster Stelle danke ich Herrn Prof. Dr. Jörn Bennewitz für die Überlassung des Themas, die fachliche Unterstützung und intensive Betreuung bei der Durchführung und Vollendung dieser Arbeit.

Ganz herzlich bedanke ich mich darüber hinaus bei Christine Baes die jederzeit gerne bereit war die Arbeit fachlich und sprachlich zu unterstützen.

Ganz besonders danke ich meiner Familie.

Nicht zu vergessen sind alle Kollegen und Freunden die mich während dieser Zeit begleitet haben und denen ich an dieser Stelle ebenfalls danken möchte.

Mein Dank gilt ebenfalls der H. Wilhelm Schaumann Stiftung zur Förderung der Agrarwissenschaften für die finanzielle Unterstützung.