A review of Quantitative trait loci in pigs[#]

R.J. Kerr[1], Y. Chen[2] and C. Moran[2]

[1]*Animal Genetics and Breeding Unit*[*]*, University of New England, Armidale, NSW*

[2]*Reprogen, Faculty of Veterinary Science, University of Sydney, NSW*

Summary

The number of known quantitative trait loci (QTL) affecting carcase and production traits is conservatively estimated as being at least 20. Many of these QTL appear to be conserved across breeds. The numbers of known QTL affecting meat quality, reproduction and disease resistance traits is less. Most QTL detection experiments have used crosses between divergent breeds. Thus many of the discovered QTL are at risk of having little relevance to commercial pig populations, since favourable alleles may already be fixed due to selection. Comparative mapping will reciprocally benefit both pig and human genetic research with sequence information flowing one way and functional information the other. For example, the recent discovery of the causal mutation for the *RN* locus has implications for human diabetes research.

Keywords: QTL, candidate genes, pigs

Introduction

The pursuit of QTL for economically important traits in pigs has motivated a large international effort in porcine gene mapping, which commenced in earnest in about 1990. While there has been considerable willingness to collaborate internationally on the development of the tools for QTL mapping, including free exchange of microsatellite markers, detailed marker map information and even advanced tools like radiation hybrid mapping resources, there is much less willingness to share information on QTL themselves. Some publicly funded QTL mapping projects in Sweden, the USA, Germany and France have put a limited amount of QTL data into the public domain, but most QTL projects, including those in Australia, are constrained by confidentiality requirements. Thus the list of QTL summarised in this review is by no means complete since many QTL have been kept secret.

The discovery of new microsatellites is still proceeding. It is estimated that a further 1500 (2000 are presently mapped) will be released to the public domain in the current year (Lee Alexander, personal communication). Over the next 5 years the single nucleotide polymorphism (SNP) will become the 3rd generation marker. Recently the USDA pig

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genome research group at Clay Center in Nebraska unveiled an ambitious SNP discovery plan (Fahrenkrug *et al.* 2000). SNPs associated with expressed sequence tags (ESTs) orthologous to genes with known human map positions will be integrated into existing linkage maps. These SNPs will provide a useful resource for linkage disequilibrium mapping, particularly since a very large number of them will eventually be characterised and placed in the public domain.

The results of published QTL mapping and association studies are summarised in Tables 1 to 4. An association study is an attempt to isolate the causative gene for a QTL phenotype. In nearly all cases reported it still cannot be confirmed the named candidate gene is causative rather than linked. To achieve brevity only QTL that reached the reported genome wide 5% signficance threshold are included, unless the QTL is of particular interest. Some studies essentially confirm and expand on results of an earlier study (e.g. Knott *et al.* 1998 and Marklund *et al.* 1999 confirm Andersson *et al*. 1994). In such cases QTL identified in the earlier study will not be listed. An abbreviated description of the experimental resource used to characterise the QTL/candidate gene is given (e.g. F2 WB x LW = F2 progeny of Wild Boar crossed to Large White). Table 5 lists the breed codes.

Production and carcase

QTL affecting production and carcase traits are listed in the Table 1. A notable entry of this table is the study of Walling *et al.* (2000). A joint analysis of data from independent QTL mapping studies in England, America, Germany, France, Netherlands, Sweden and Czech Republic provided definitive evidence for QTL on SSC4 affecting backfat (BFT), birthweight (BW0) and lifetime average daily gain (ADG3), demonstrating the benefit of such collaboration. Other notable entries in this table are the two studies that successfully identified *IGF2* as a candidate gene for QTL affecting muscle mass and fat deposition on SSC2. Both studies confirmed that the gene is expressed exclusively from the paternal allele. Dutch researchers have demonstrated the *HFABP* gene on SSC6 is a candidate gene for QTL affecting backfat, slaughter weight and intramuscular fat (IMF) (see Table 2) in Duroc populations. However, recent Australian (Chen *et al.* submitted) and Austrian (Nechtelberger *et al.* submitted) studies found no affect of *HFABP* gene variants on IMF or BFT in Large White and Landrace breeding populations in these two countries. These results imply one of several possibilities. The Dutch results may be due to linkage disequilibrium between the *HFABP* and another unknown locus. Alternatively, variable effects of the *HFABP* locus may exist in different genetic backgrounds, or, the Australian and Austrian populations could be fixed for a causative mutation in the *HFABP* gene.

Chromosomes 7 and 13 occur frequently in studies detecting QTL affecting production and carcase traits. The pig major histocompatibility complex (SLA) spans the centromere of chromosome 7. Restriction fragment length polymorphisms (RFLP) of SLA class 1 genes have been found to be associated with variation in ADG in the Duroc breed (Jung *et al.* 1989). Nielsen *et al.* (1996) associated polymorphism in the promotor of the aminopeptidase N (*ANPEP*) locus with significant changes in daily gain in various Danish pig breeds. This gene maps to the region containing the QTL identified in the studies of Rothschild *et al.* (1995), Rohrer and Keele, (1998a) and Milan *et al.* (1998).

Nystrom *et al.* (1997) observed significant associations between the blood protein transferrin (*TF*) genotypes and early body weight. The *TF* locus is located adjacent to the *PIT-1* locus, a regulatory factor for growth hormone, which Yu *et al.* (1995) showed to be significantly associated with birth weight. *PIT-1* has the same map position as the QTL for birth weight reported by Knott *et al.* (1998). Chromosome 12 is significant for containing the growth hormone (*GH*) gene. In demonstrating the *GH* gene is a QTL for growth rate, Nielsen *et al.* (1995) provide only suggestive evidence, while results in Casas-Carillo *et al.* (1997) were inconclusive.

Table 1. QTL and candidate genes affecting production and carcase quality traits

Locus	Chrom	Trait	Resource	Reference
QTL	1	BW0	F2 WB x LW	Knott *et al.* 1998
QTL	1	ADG1, ADG2, ADG3	F2 MS x YS	Paszek *et al.* 1999
QTL	1	BFT, TPP	F2 MARC	Rohrer and Keele 1998a,1998b
QTL	1	BW0, ADG2	F2 MS x GO	Wada *et al.* 2000
QTL	2	ADG3	F2 BS x YS	Malek *et al.* 2000
QTL	2	ADG3	F2 WB x LW	Knott *et al.* 1998
IGF2	2	SMM, BFT	F2 LW x PT	Nezer *et al.* 1999
IGF2	2	SMM, HMM	F2 WB x LW	Jeon *et al.* 1999
QTL	2	TPP	F2 WB x LW	Andersson-Eklund *et al.* 1998
QTL	3	BST	F2 MS x GO	Wada *et al.* 2000
QTL	4	BFT, CL	F2 WB x LW	Marklund *et al.* 1999
QTL	4	BFT, AFT, IL, ADG3	F2 WB x LW	Knott *et al.* 1998
QTL	4	BW1	F2 MS x YS	Paszek *et al.* 1999
QTL	4	BFT, ADG3	IO	Wang *et al.* 1998
QTL	4	BFT, ADG3, FCR	WB x PT, MS x PT	Moser *et al.* 1998
QTL	4	BFT, BW0, ADG3	COMBINED DATA	Walling *et al.* 2000
IGF1	5	ADG2	YS, HS, LR	Casas-Carrillo *et al.* 1997b
GPI	6	ADG 2	DU, LR	Clamp *et al.* 1992
H-FABP	6	BFT, BWS	DU	Gerbens *et al.* 1997
QTL	6	BFT	F2 WB x PT, MS x PT	Moser *et al.* 1998
QTL	6	BFT, EMA	F2 IB x LR	Ovilo *et al.* 2000
QTL	7	BFT, LEA, BW0	IO	Rothschild *et al.* 1995
QTL	7	BFT, BW6	LW x MS	Milan *et al.* 1998
QTL	7	BFT, CW, CL	F2 MARC	Rohrer and Keele 1998a,1988b

QTL	7	BFT	F2 MS x GO	Wada *et al.* 2000
QTL	7	BFT	F2 MS x LW	Rattink *et al.* 2000
ANPEP	7	ADG2	DU, HS, YS, LR	Nielsen *et al.* 1996
SLA RFLP	7	ADG3	DU	Jung *et al.* 1988
QTL	9	BW0, ADG1	F2 MS x GO	Wada *et al*. 2000
MYOGENIN	9	ADG, BW0	YS	Tepas *et al.* 1999
QTL	10	ADG2	F2 WB x LW	Knott *et al.* 1998
QTL	10	BW0, ADG2	F2 MS x GO	Wada *et al.* 2000
QTL	12	BW0	F2 WB x LW	Knott *et al.* 1998
GH	12	BFT	F2 WB x PT	Knorr *et al.* 1997
QTL	13	BW0, ADG1	F2 WB x LW	Knott *et al.* 1998
QTL	13	ADG1	F2 WB x PT	Moser *et al.* 1998
PIT1	13	BW0, BFT	IO	Yu *et al.* 1995
TF	13	BW6, BW9	YS	Nystrom *et al.* 1997
QTL	X	BFT	F2 MS x LW	Harlizius *et al.* 2000

BW0 = body weight at birth; BW1, BW6, BW9 = body weight at 1, 6 and 9 weeks; BWS = body weight at slaughter; ADG1 = average daily gain to test; ADG2 = average daily gain over test; ADG3 = lifetime average daily gain; BFT = back fat; AFT = abdominal fat; BSN = backskin thickness; SMM = skeletal muscle mass; HMM = heart muscle mass; EMA = eye muscle area; CL = carcase length; CW = carcase weight; IL = intestinal length; LEA = loin eye area; TPP = trimmed product %; FCR = food conversion rate.

Table 2. QTL and candidate genes affecting meat quality traits

Locus	**Chrom**	**Trait**	**Resource**	**Reference**
QTL	2	WHC, pH	F2 WB x LW	Andersson-Eklund *et al.* 1998
QTL	2	WHC, COL, DP, TEN, FIR	F2 BS x YS	Malek *et al.* 2000
RYR1	6	PSE	F2 WB x PT, MS x PT	Geldermann *et al.* 1996
H-FABP	6	IMF	DU	Gerbens *et al.* 1997
H-FABP	6	IMF	F2 MS x LW (LR)	Gerbens *et al.* 2000
QTL	6	IMF	F2 IB X LR	Ovilo *et al.* 2000
QTL	7	AND	F2 MS X LW	Milan *et al*. 1998
PRKAG3	15	WHC,COL, pH, HAM	HS	Milan *et al.* 2000
QTL	X	IMF	F2 MS X LW	Harlizius *et al.* 2000

WHC = water holding capacity; COL = meat colour; DP = dressing percentage; TEN = tenderness score; PSE = pale soft exudative pork; IMF = intramuscular fat content; pH = pH of meat; HAM = % of lean meat in leg; AND = androstenone level

Meat quality

The significance of the skeletal muscle ryanodine receptor gene (*RYR1*), more commonly referred to as the *HAL* gene, on pork quality has been well established (Geldermann *et al.,* 1996). The discovery of a mutation in the *PRKAG3* gene is a recent major success in animal genetics. The Hampshire effect of "acid meat" was first recognised by Naveau (1986) who put forward the hypothesis of a single major gene (the *RN* gene after Rendement Technologique NAPOLE). This hypothesis was strengthened by segregation analysis of phenotypic data (Le Roy *et al.,* 1990). Reinsch *et al.* (1997) linkage mapped the *RN* gene to chromosome 15. A major collaborative effort involving three countries undertook the task of positionally cloning the gene. They first constructed a BAC contig of the *RN* region. This was used to develop new markers and facilitated the progression from low-resolution genetic map to high-resolution radiation hybrid map. Linkage disequilibrium analysis revealed two markers that most likely defined the haplotype associated with the gene. The BAC clone containing these markers was randomly sequenced. BLAST searches revealed a coding sequence with sequence similarity to isoforms of the AMP-activated protein kinase (AMPK) gene. Mutation analysis of *PRKAG3*, the isoform most likely regarded as the *RN* gene, revealed a SNP which was exclusively associated with *RN*-. This dominant mutation inhibits AMP activation, resulting in increased glycogen content in skeletal muscle. This discovery has repercussion on diabetes research and sports medicine, disproving the notion that animal genetics research benefits from human research and not vice versa. The *RN* discovery also serves as a paradigm for future research. Elsewhere in Table 3, the QTL on chromosome 7 affecting androstenone levels in fat has significance for boar taint research, while the QTL detected on chromosome 2 affecting various meat quality traits prioritises the relevant regions for future fine mapping studies.

Table 3. QTL and candidate genes affecting reproduction traits

Locus	**Chrom**	**Trait**	**Resource**	**Reference**
ESR	1	litter size	MS, LW	Rothschild *et al.* 1996
RARG	5	litter size	LW	Messer *et al.* 1996
QTL	8	ovulation rate	F2 MS x YS	Wilkie *et al.* 1999
QTL	8	ovulation rate	F2 NE	Rathje *et al.* 1997
QTL	8	ovulation rate	F2 LW x MS	Milan *et al.* 1998
RBP4	14	litter size	LW	Messer *et al.* 1996
PRLR	16	litter size	LW, DU, LR	Vincent *et al.* 1998
MTNR1A	17	litter size	LW	Ollivier *et al.* 1997

Reproduction

QTL for increased ovulation rate have been identified on chromosome 8. The map positions of QTL identified by Rathje *et al*. (1997) and Milan *et al*. (1998) concur, but are some distance away from the position of the QTL identified by Wilkie *et al.* (1999). The favourable allele of the estrogen receptor (*ESR*) locus has been significantly associated with increased litter size in Meishan and Large White breeds (Rothschild *et al.* 1996). The disparity of the effect between breeds (0.42 pigs/litter in LW and 1.15 pigs/litter in MS) suggests genetic background is an important factor in the expression of this gene. Gene frequency changes in alleles at the melatonin receptor 1A (*MTRN1A*) locus following selection for profligacy suggests this locus may also be a determinant of increased reproductive capability (Ollivier *et al.* 1997). Messer *et al.* (1996) have associated the Retinol-Binding Protein 4 (*RBP4*) gene with increased litter size in Large White, while Vincent *et al.* (1998) have associated the prolactin receptor gene (*PRLR*) with increased litter size in various PIC lines. Additional data is needed in each case to confirm the observed effects.

Table 4. QTL and candidate genes affecting disease resistance and miscellaneous traits

Locus	**Chrom**	**Trait**	**Resource**	**Reference**
QTL	1	vertebrate and teat number	F2 MS x GO	Wada *et al.* 2000
QTL	2	vertebrate number	F2 MS x GO	Wada *et al.* 2000
IGF2	2	heart weight	F2 WB x LW	Jeon *et al.* 1999
QTL	2	proliferation	F2 WB x LW	Edfors-Lilja *et al.* 2000
QTL	5	IgG titers to K88	F2 WB x YS	Edfors-Lilja *et al.* 1998
QTL	6	IgG titers to 0149	F2 WB x YS	Edfors-Lilja *et al.* 1998
QTL	6	IL-2 activity	F2 WB x LW	Edfors-Lilja *et al.* 2000
FUT1	6	ECF18 resistance	LR	Meijerink *et al.* 2000
MSHR	6	black spotting	F2 WB x LW	Mariani *et al.* 1996
QTL	7	glucose and cortisol level	F2 LW x MS	Milan *et al.* 1998
KIT	8	white coat color	LR, DU, LW, HS, MS	Johansson Moller *et al.* 1996
QTL	8	neutrophil number	F2 WB x LW	Edfors-Lilja *et al.* 2000
QTL	12	IL-2 activity	F2 WB x LW	Edfors-Lilja *et al.* 2000

Disease resistance and miscellaneous traits

The companion studies of Edfors-Lilja *et al.* (1998, 2000) provide the sole QTL scans for disease resistance or immune response. The earlier study showed significant QTL on chromosomes 5 and 6 affecting serum IgG antibody response to *E. coli* antigens. The latter study monitored leukocyte numbers and functions in pigs before and after external stressors were imposed. A significant QTL on chromosome 8 was found to influence induced alteration in numbers of neutrophils. A significant QTL affecting mitogen-induced proliferation was detected on chromosomes 2 and significant QTL affecting IL-2 activity were detected on chromosomes 6 and 12.

Research has shown that adhesion of F18 fimbriated *E. Coli* (ECF18) to intestinal mucosa causes oedema disease in piglets. The gene controlling expression of the ECF18 receptor, *ECF18R*, has two alleles *B* and *b*, representing susceptibility and resistance to adhesion, respectively. With linkage analysis Meijerink *et al.* (1997) have shown polymorphisms at the locus encoding the alpha-1 fucosyltransferase enzyme (*FUT1*) to be less than 1 cM from the *ECF18R* locus. In an extension of this work Meijerink *et al.* (2000) showed in a sample of pigs the guanine and adenine variants at nucleotide 307 were 100% correlated with the $ECF18R^B$ and $ECF18R^b$ alleles, respectively. This research supports the assumption *FUT1* and *ECF18R* are the same gene. Klukowska *et al.* (1999) found a high frequency of the adenine variant at nucleotide 307 in a sample of Polish Zlotnicka pigs, while finding lower frequencies in Large White and Landrace samples. This suggests indigenous breeds are a valuable source of genes causing resistance to specific pathogens. The evaluation of genes responsible for determination of coat colour has been important for biological and economic reasons. The work has contributed to the development of a comparative map for chromosome 6. Also elite young boars can now be tested for some unfavourable recessive colour alleles. Testing is important because penalties for coloured carcases can be substantial.

Table 5. Explanation of breed and resource codes used in Tables 1 – 4.

Code	Description	Code	Description
BS	Berkshire	MS	Meishan
DU	Duroc	PT	Pietran
HS	Hampshire	WB	European Wild Boar
LR	Landrace	YS	Yorkshire
LW	Large White	GO	Gottingen miniture
IB	Iberian		
IO	Iowa State University resource. Three generation pedigrees making use of diverse crosses involving two Chinese breeds (Meishan and Minzhu) and three American breeds (DU, HS, LR)		
NE	University of Nebraska resource. F2 high ovulation line x control. Each line derived from same base (F3 LW x LR)		
MARC	U.S. Meat Animal Resource Center resource. F1 MS x LW females backcrossed to MS and LW boars		

Conclusions

The *RN* project will undoubtedly be the model for future gene discovery. Segregation analysis, followed by linkage analysis using framework genetic maps, will continue to play vital preliminary roles. Positional cloning of causative genes for QTL phenotypes will remain the greatest challenge. International collaboration will help in overcoming limited resources faced by animal geneticists. The near complete human and mouse transcript maps will compensate for the poorly developed transcript maps in the pig, provided there is extensive linkage conservation between species. Johansson *et al*. (1995) have shown this is true in the case of the pig and the human genomes.

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