QTL detection and utilisation in pigs

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Introduction

At least 40 QTL studies have been reported in pigs (Andersson et al., 1994 a,b; Andersson-Eklund et al., 1998; Beeckmann, 2000; Bidanel et al., 2001; Cassady et al., 2001; Casas-Carrillo et al, 1997; Ciobanu et al, 2001; De Koning et al., 1999; De Koning et al., 2000; De Koning et al., 2001a,b; Desautes et al., 2002; Edfors-Lilja et al., 1998; Geldermann et al., 1999; Grindflek et al., 2001; Harlizius et al, 2000; Hirooka et al, 2001; Knott et al., 1998; Knott et al., 2002; Malek et al., 2001a,b; Marklund at al., 1999; Nezer et al, 2002; Paszek et al., 1999; Paszek et al., 2001; Pérez-Enciso et al., 2000 ; Quintanilla et al., 2002; Rathje et al., 1997; Rattink et al., 2000; Rohrer, 2000; Rohrer and Keele, 1998a,b; Rohrer et al., 1999; Rothschild et al, 1995; Short et al., 1997; Wada et al., 2000; Walling et al., 1998; Walling et al., 2000; Wang et al., 1998; Wilkie et al., 1999; Yu et al, 1999) with most being full genome scans. Most have been reviewed by Bidanel and Rothschild (2002). These studies have detected QTLs affecting growth, fatness, muscularity, reproduction, meat quality, immune function and other traits. Most have employed wide crosses between very genetically distinct breeds or populations to generate their mapping resources. Generally these wide-cross resource pedigrees use at least one non-economic breed of pig, such as Wild Boar or Meishan, and this raises some issues about the relevance of the QTLs detected to commercial populations of animals. Nevertheless there is no doubt that these studies have generated an enormous amount of useful information in their own right and have paved the way for studies on more commercially relevant populations of animals. An excellent example of such information transfer is provided by Ciobanu et al (2001) who worked from the discoveries by Malek et al (2001b) of QTLs for glycogen content in muscle and associated meat quality in a Berkshire x Yorkshire cross pedigree through to the identification of novel mutation in the protein kinase adenosine monophosphate-activated gamma(3)-subunit (PRKAG3) gene segregating in commercial populations of pigs and having an appreciable effect on meat quality.

Of course it is possible to evaluate effects discovered in wide cross resource pedigrees in Australian populations of pigs, providing that we have a resource pedigree which is performance tested for the relevant traits. In fact, performance testing is almost always the limiting factor, as the collection of DNA and genotyping of markers from the relevant region is reasonably straightforward. However breeding the resource and collecting the performance test results requires considerable time and expense.

As an example of the scale of the wide-cross mapping efforts, Professor Herman Geldermann's laboratory will shortly be publishing a detailed report, consisting of 20 papers, being one for each chromosome plus a large overview paper (Geldermann et al, in press) taking up an entire issue of *Journal of Animal Breeding and Genetics*. This work, involving collaborators from Germany, Czech Republic, Poland, Italy, Singapore

and Australia, is based on three large F2 resource pedigrees bred in Germany from Pietrain, Meishan and Wild Boar founder populations. Numerous QTLs have been discovered throughout the genome, many of them novel, and many other fascinating aspects of the genetics of pigs have been confirmed or will be reported for the first time. For example, the study confirmed previous reports of substantial sex and chromosome specific variation in recombination rate, with female recombination rates consistently higher than male on most but not all chromosomes. Another fascinating finding was that the X chromosome appears to harbour a disproportionately high number of QTLs compared with the autosomes. The Hohenheim study was the one of the first in animals to detect "cryptic QTLs" where the effect of the QTL allele is unexpected in relation to the phenotype of the parents. For example, on chromosome 7, there is a QTL where Meishan, a very fat breed, have an allele which reduces fatness, compared with the allele inherited from the very lean Pietrain breed. Such cryptic QTLs confirm the presence in low performing breeds or populations of very useful genes. For plant breeders, most useful novel genetic variation is now being sought as cryptic variation from non-economic lines.

QTL studies described by De Koning et al (2000) have found that imprinting is widespread and important in quantitative inheritance in pigs. That the effect of a gene can depend on whether it is inherited maternally or paternally has been a fascinating and unexpected revelation in mammalian biology. It will be very interesting to know, as our knowledge of the prevalence and effects of imprinting increase, whether we will need to take imprinting into account in designing breeding programs of the future. Will PIGBLUP of the future require an "imprinting module"?

In Australia, we have never had the opportunity to create wide-cross resource pedigrees for QTL mapping (hence our minor involvement in the German study) and as a result we have focused the majority of our work immediately on commercially relevant populations. Instead of generating large F2 pedigrees, involving breed crosses, we have utilised large sire families to search for evidence of QTLs segregating in commercial populations at QAF (Bunge) Meat Industries. Because of the scale of the QAFMI operations, it has been possible to rapidly generate the required mapping resources under uniform conditions of husbandry and management. As is becoming increasingly common in science, the findings of these studies are constrained by confidentiality agreements, which restrict my ability to speak freely about our results. However we have found evidence for numerous QTLs for many traits in our studies and are now focussing our efforts on several QTL considered most economically relevant and most easily integrated into a comprehensive multi-trait breeding program.

What I want to discuss here are the next steps in the process? How do we get from an imprecisely mapped QTL to a precisely mapped gene and possibly even a mutation for which a genotype test can be provided and how can we transfer this to the industry?

1. High resolution mapping

Generally QTLs are mapped with about 10 to 20 cM resolution, which is not fine enough to permit effective use of the QTLs in marker assisted selection nor even their further characterisation. There is a fundamental biological problem that neither F2 resources nor large sire families have enough recombination between markers and QTLs to sufficiently resolve the positions of the QTLs by linkage mapping. This is a

problem for human and plant geneticists, as well as for animal geneticists. What has become apparent over the past few years, however is that linkage disequilibrium, that is non-random associations between alleles at different loci, is very common but only for very closely linked genes. Over long periods of time, recombination has removed all non-random associations between distantly linked loci, leaving only the associations between very tightly linked loci. So instead of depending only on recombination in the parental generation of a resource pedigree, it is possible to utilise "historical" recombination which has accrued over a very large number of generations. Ideally linkage mapping and linkage disequilibrium analysis are combined to even further improve the precision of the mapping (Meuwissen et al, 2002).

A fundamental feature of linkage disequilibrium mapping is the identification of haplotypes; effectively small chunks of a chromosome containing groups of alleles from different loci. If a haplotype can be identified bracketing a QTL, linkage disequilibrium can be exploited not only as a mapping tool but as a method for exploiting QTLs in real world improvement programs. The haplotypes can assist in the marker assisted selection (Meuwissen et al, 2002). In fact, Meuwissen, Hayes and Goddard (2001) contend that with sufficient markers, it is possible to relatively accurately determine the total genetic value for an individual by exploiting the linkage disequilibrium between markers and QTLs dispersed throughout the genome.

To put it in pictorial terms, haplotypes can be thought of as coloured flags which permanently identify particular chromosomal segments. For example, blue flags may always be associated with good QTL alleles, which we will want to retain, and purple flags with bad QTL alleles, which we want to eliminate from the population. The relationship is constant. For linked markers identified in family studies, the blue flag may change from being associated with a good allele to a bad allele due to recombination. Thus we must continue to monitor the relationship between QTL and markers in different families and different generations if using linked markers which are not in linkage disequilibrium with the QTL. This is much more work and expense.

2. Comparative mapping

The ultimate genetic marker for a QTL is the mutation in the gene responsible for the observed QTL effect. If you have found the mutation, you can forget about linked markers and even haplotypes – you have all you need for implementation of molecular genotype assisted selection. The halothane mutation genotyping program throughout the world has shown the pig industry just how successful this can be. Unfortunately the genome of the pig is relatively poorly characterised and even if we know where to go looking in the porcine genome for the gene underlying a QTL, we have very few mapped candidates to search among. However the human genome is complete and contains a complete (or very nearly complete) sequence of all genes in order along all chromosomes. We have a rough idea of the relationship between pig and human chromosomes, but now have the job ahead of us of improving our knowledge of the details.

In our project at the University of Sydney during 2002, we refined the comparative map of pig chromosome 10 (SSC10) with respect to relevant human chromosomes (Aldenhoven et al, submitted) because we had QTLs of particular interest on them. By refining the comparative maps, we could narrow down our search for comparative

positional candidates among the human genome sequence. Unfortunately at the current level of resolution of QTL mapping, this still leaves us with hundred of positional candidates, many of which are poorly annotated and whose biochemical function is poorly characterised. Thus refining the position of the QTL, as described above, must go hand in hand with the search for candidates underlying the QTL effects.

For example, we already knew from ZOO-FISH mapping that human chromosomes (HSA) 1, 9 and 10 share regions of homology with pig chromosome 10 (SSC10). We took human genomic sequence from relevant chromosomal regions of the public human genome sequence and systematically searched porcine EST databases to identify sequence from the equivalent (but otherwise uncharacterised) porcine genes. This sequence enabled us to design primers which we then used to map the pig genes, either at low resolution using a somatic cell hybrid panel or at very high resolution using a radiation hybrid mapping panel. Twenty six genes were mapped in this way from HSA1, 9 and 10, with 13 mapping to SSC10, 11 to SSC1 and two to SSC9 (Figure 1). At the end of this exercise, we had a much better picture of the relationship between these porcine and human chromosomes and were better able to gauge where we should be looking in the human sequence for our candidates (Figure 2). A spin-off benefit of course, is that we were substantially improving the porcine map and identifying potential loci in which we could identify polymorphisms for building haplotypes across regions of interest

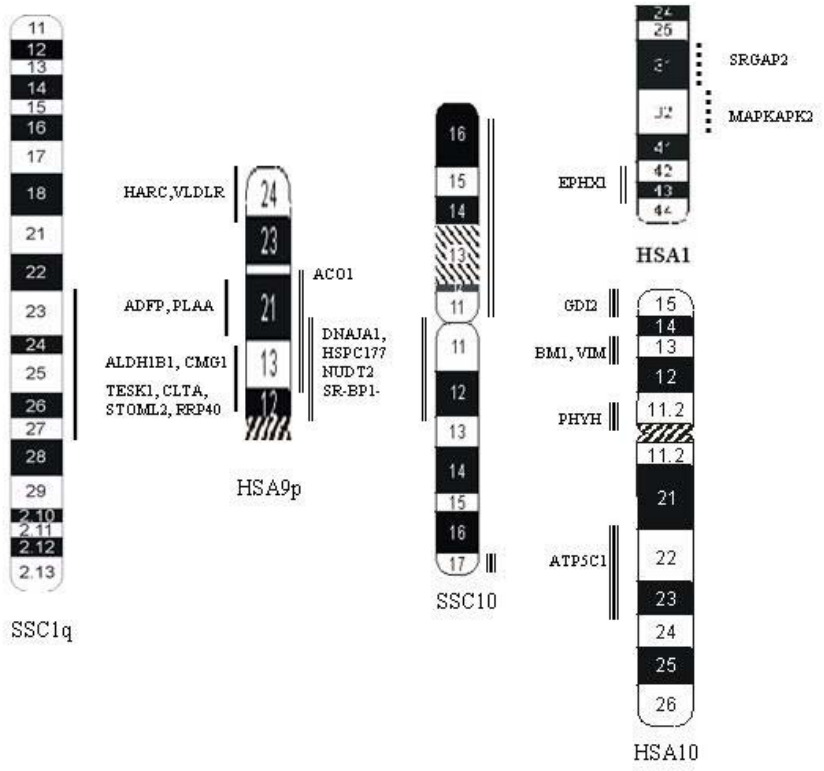

Figure 1 Comparative mapping of 25 genes using a somatic cell hybrid panel to assist in the search for candidates loci from the human genome sequence. The inferred regions of homology between porcine and human chromosomes are indicated with line symbols: SSC1q and HSA9p, single line; SSC10q and HSA9p, double line; SSC10p

and HSA1q, thick and thin double line; SSC10q and HSA10, triple line; SSC9 and HSA1, dotted line. (Aldenhoven et al, submitted). The letter "p" indicates "short arm" and "q" indicates "long arm". The short arm is normally shown at the top of each chromosome graphic.

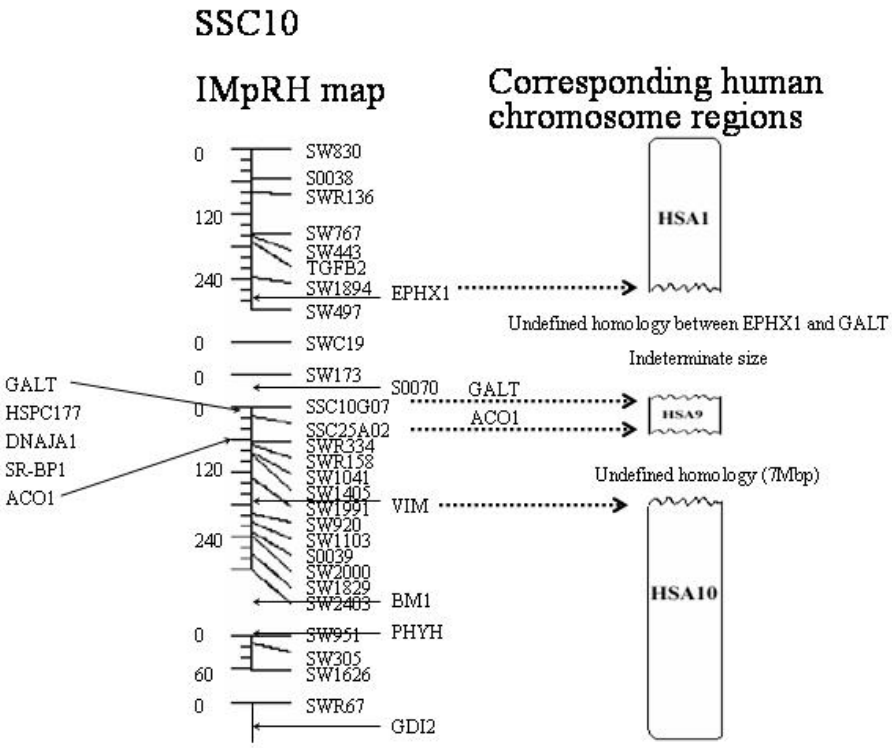

Figure 2 A more detailed representation of the relationship we have determined between pig chromosome 10 and three human chromosomes, indicating regions of SSC10 where cross species homology requires further elucidation. The porcine radiation hybrid map positions are shown (Aldenhoven et al, submitted).

3. Implementation of the discoveries of QTL mapping

Hayes and Goddard (2002) have shown for realistic models of pig improvement programs that the use of linked markers will provide only limited and probably not economically justifiable benefits in improving selection responses. However recognition of haplotypes of markers bracketing QTLs can in theory provide almost all the benefits of recognition of the locus and mutation responsible for the QTL effects (Meuwissen et al, 2001), albeit with a somewhat higher laboratory cost in genotyping and with the risk of breakdown of the initially recognised linkage disequilibrium relationships between markers and QTLs.

Thus our immediate objective is therefore to identify haplotypes bracketing QTLs of primary interest and to introduce genotyping for these haplotypes to the industry.

How close are we to identifying such haplotypes? We are currently moving from the phase of initial QTL discovery, with about 20cM resolution of our QTL positions, to what we hope will provide about 2cM resolution of the QTL position. To achieve this order of magnitude improvement in precision of map position, we are developing a new linkage disequilibrium mapping resource at QAFMI consisting of 3,000 animals to which we will be applying selective genotyping of markers at about 1 cM intervals across the regions of interest. This should enable effective mining of the human sequence for sufficient flanking markers to enable construction of an efficient haplotyping system, using either microsatellites or single nucleotide polymorphisms (SNPs) in the flanking gene loci. Of course, this will also set us on the track of the underlying gene/mutation responsible for the QTL effect, an important objective as it will yield easily protectable IP. However our primary objective will be to develop the haplotype of markers for implementation. Linkage disequilibrium is a mixed blessing in that it enables mapping of QTLs to high precision, but then has the potential to seriously interfere with subsequent recognition of the gene causing the QTL effect, due to the bracket of non-randomly associated gene loci. So recognition of the underlying gene locus will be a non-trivial task.

4. Industry contribution to QTL mapping

While QAFMI continues to make an excellent and extremely valuable contribution to our gene mapping efforts, we are very keen to have as much of the industry as possible engaged in providing additional resources for QTL mapping. Thus we are keen to tap into potential resources, which could be provided by breeders. To do this, we require not only access to performance and pedigree records, but DNA samples. With the move towards linkage disequilibrium mapping, the value of large resources of this sort, which do not necessarily involve sampling of animals of close familial relationship, is becoming increasingly important. We are planning methods for sampling and storing DNA from AI boars, purified from semen samples. Since DNA yields from semen are high, only small amounts of semen are necessary to develop an archive of DNA samples for future analysis. One obvious source of samples is NPIP. However a substantial limitation of the current NPIP resource is the small number of traits performance tested on the NPIP boars and the fact that some of these, such as backfat are very amenable to conventional performance-based selection, with less potential to benefit from molecular selection methods. Thus we are keen to investigate the possible inclusion of other traits, such as meat quality and food conversion efficiency, to extend the value of such an industry resource. Providing that we have performance records or estimated breeding values to relate to DNA samples, the resource could be a valuable mechanism for testing the existence and relevance of QTLs discovered by other groups and for QTL discovery. Industry needs for performance testing should drive the measurements, rather than perceived scientific needs for QTL evaluation. In any case, large numbers of samples will be crucial in constructing such a resource and the sooner we start it, the better in the long run.

Conclusions

The international community of pig geneticists has advanced a long way in the recognition of chromosomal regions affecting variation in economically important traits in pigs, with large numbers of published reports and probably even more unpublished

studies on QTLs for a wide range of traits. What is now happening is the refinement of map position as a prelude to implementation of the QTLs in breeding programs, either via a haplotype/linkage disequilibrium approach or the direct identification and genotyping of mutations in genes affecting these traits. Our immediate objective is to develop a haplotype marker system for a QTL for an economically important trait in pigs and we are currently mustering the resources, both animal and genomic, to achieve this.

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