THE ROLE OF MAJOR GENES AND DNA TECHNOLOGY IN SELECTION FOR MEAT QUALITY IN PIGS

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ABSTRACT

The aim of this paper is to discuss the role of major genes and DNA technology in selection for meat quality in modern breeding schemes. An overview of major genes, including genes that affect water-binding, colour, marbling, boar taint and tenderness, is given. Two different approaches for the development of DNA tests as selection tools are described: (1) localization of relevant genes on the genome map using DNA markers, and (2) research on mutations in targeted functional genes (candidate genes). It is concluded that major genes for meat quality provide excellent opportunities, not only for increasing the level of meat quality, but also for decreasing variability. Furthermore, major genes can be exploited for differentiation for specific markets. It is stressed that phenotypic data on culled nucleus animals provide an important basis for the development of DNA tests for selection for meat quality. More fundamental research is recommended to understand the interactions of genes with each other and with environmental factors.

INTRODUCTION

Breeding schemes for meat animals have so far focused on farm performance traits and carcass quality. This has resulted in substantial improvements in traits like lean/fat ratio, prolificacy, growth rate and feed efficiency. Rates of annual improvement in pigs have been 1 to 2% per year (De Vries and Kanis, 1994). Spectacular improvements have also been realised in other species, especially chicken (Havenstein et al, 1994). Relatively simple performance test data have been the basis for these improvements, and the traits selected for were assumed to be influenced by a large number of genes each of small effect (infinitesimal gene model).

At present, we see important changes in breeding strategies. First, the breeding goal of some of the breeding organizations starts to include meat quality attributes in addition to the "traditional" production traits (Stewart, 1998). Secondly, evidence is accumulating that current and new breeding goal traits may involve a relatively small number of genes with relatively large effects (known as major genes) as opposed to the infinitesimal model that we have relied on so far. Modern DNA-technologies provide the opportunity to exploit these major genes, and this approach is a very promising route for the improvement of meat quality, especially since direct meat quality assessment is not viable for potential breeding animals.

The aim of this paper is to discuss the role of major genes and DNA technology in selection for increased meat quality and uniformity. After giving an overview of relevant major genes detected by segregation analysis and the approaches to use DNA technology, the discussion will focus on how these new opportunities can be exploited optimally in selection schemes.

SEGREGATION ANALYSIS

Geneticists consider that a gene can be defined a major gene, when the difference between the mean value of the individuals homozyguous for this gene and that of individuals not carrying this gene, is equal or superior to one phenotypic standard deviation of the trait of interest. Genes with such large effects can usually be detected by analyzing phenotypic data across families where the gene segregates. This approach is referred to as segregation analysis. Sellier and Monin (1994) reviewed two important major genes that affect pig meat quality: Halothane and RN. After a short update on these two genes, two more recent examples for pigs will be provided.

Halothane Sensitivity Gene

This gene has been studied and discussed extensively. A thorough review is given by Sellier and Monin (1994) and results of Larzul et al (1997) and a review of Hermesch (1997) add interesting material to the discussion. The gene started to become relevant for breeders when Christian (1972) speculated the existence of monogenic variation in stress-susceptibility and when

Eikelenboom and Minkema (1974) showed that the stress syndrome could be triggered by halothane gas. Since then, many comparisons regarding meat quality were done, and most studies showed major differences in pH, colour and waterbinding between stress positive and negative pigs. These differences were directly related to a large difference in PSE (Pale Soft Exudative meat) incidence between the two genotypes.

Since 1991 we can accurately separate all three Halothane genotypes (instead of just reactors (nn) from non-reactors (NN and Nn)) with the Hal1843™[1] DNA test. This test was developed from the work of Fujii et al (1991) who found the causative mutation for porcine stress syndrome in the gene encoding the ryanodine receptor or calcium release channel (CRC1). Once it was possible to easily detect heterozyguous animals, more detailed work on the effect of this mutation was possible.

A major discussion at present is whether carriers have acceptable meat quality compared to the animals that are completely free of the gene. This is very relevant, since the gene definitely improves carcass lean content. No general conclusion from this discussion is possible, since the optimum approach depends on slaughter conditions and the type of processing (eg cooked vs. dried vs. fresh). The best strategy for breeding organizations is to make sure that all the dams of the slaughter pigs are free of the Halothane gene, whereas the Hal-status of the sires can be tailored.

RN⁻gene

The RN⁻gene was first suggested by Naveau (1986) and later confirmed by segregation analysis in two French composite lines of pigs (LeRoy et al, 1990) as a gene with dominant inheritance. The recessive allele leads to a decreased technological quality due to a lower meat protein content and reduced ultimate pH. The latter is a result of an increased glycogen content in the white (fast-glycolytic) fibres. For (low phosphate) cooked ham processing, the yield of RN- carriers is 5-6% lower, and moreover these hams can have extremely high slicing losses. So far, the gene has been found segregating only in populations with Hampshire influence, but because of its dominant inheritance and the widespread use of Hampshire derived sires, the gene is very relevant for breeders.

Milan et al (1995) found that the gene is located on chromosome 15 and later DNA marker studies (Milan et al, 1996; Mariani et al, 1996; Looft et al, 1996) mapped the gene more accurately. The most recent published results place RN between Sw2053 and Sw936, a bracket of approximately 8cM (Milan et al, 1996). However, Milan and his colleagues have subsequently reduced this distance with new markers (pers. comm.). Based on the map position, a commercial DNA-marker test for detecting the gene was developed and validated (De Vries et al, 1997). The test successfully predicted large differences in ultimate pH and phosphate free ham processing yield. The study also showed that the yield differences completely disappeared when phosphate was used. Although the test is an excellent tool to quickly reduce the incidence of the gene, its complete elimination requires a DNA probe that detects the causative mutation.

Intramuscular fat

Intramuscular fat (IMF) has been identified as playing a role in eating quality of pork.

Janss et al (1994; 1997) performed a segregation analysis on meat quality data of F2 crosses between Meishan and Dutch pig strains. They detected a recessive major gene for IMF, originating from Meishan. Animals with two copies of the gene had an average of 3.9% IMF in the loin, whereas carriers and homozyguous negative animals had 1.8%. Research is underway to look at the existence of this gene in purebred populations, eg Duroc (Monin et al, 1998). This could eventually lead to DNA tests that allow better control of the marbling level of pork. Breeders will then have a large influence on the level of this trait, since its heritability is around 50% (Cameron, 1990; Hovenier et al, 1993; De Vries et al., 1994). The challenge is to achieve a higher IMF without increasing the levels of the other fat depots (subcutanuous, abdominal and intermuscular). More attention to this is given in the Candidate Gene section of this paper (H-FABP gene).

Androstenon

Another trait with a high heritability is the level of androstenone (Willeke, 1993), which is one of the causes of the so-called 'boar taint' problem in meat from entire males (Bonneau, 1997). Applying segregation analysis, Fouilloux et al (1997) found a

[1]The Hal- 1843™ is licensed from the Innovations Foundation, Toronto, Canada, owner of the trademark

major gene for androstenone level in LW populations that were selected on this trait. The gene giving rise to a low androstenone level was dominant, and carriers of this gene had 3 standard deviation (SD) units lower level than non-carriers (0.33 vs. 0.9 ppm). In the same data set, the authors also found a major gene for the development of the bulbo-urethral glands. The size of these glands are seen as a good indicator of the sexual maturity status of boars (Fouilloux et al, 1997).

Earlier work in France (Bidanel et al, 1996) showed a large gene effect on androstenone level in an F2 generation of Meishan with Large White. This gene effect was linked with the major histocompatibility complex of the pig (SLA). Linkage with SLA haplotypes was also shown with male genetical tract development in work by Rothschild et al (1986).

Boar taint is not only caused by androstenone, but also by skatole. Genetic work on skatole levels is limited. However, this trait also shows some genetic variation, and Lundstr^m et al (1994) suggested, based on work in experimental Yorkshire lines, that the genetic effect on skatole may be due to a major gene with a recessive mode of inheritance. They expect that the expression of the gene depends on certain environmental conditions like diet composition and hygiene.

DNA TECHNOLOGY

The evidence for major genes reported in the previous section was originally obtained using segregation analysis, i.e. without any DNA marker information. Afterwards molecular studies were performed to detect the location of these genes on the genetic map. In practice, and except for alleles of very large effect, DNA studies are required to dissect the genetic nature of most traits of economic importance. In this section an overview of the latest results is given. The first part deals with DNA markers that are closely linked with major genes. The second part deals with mutations in targeted functional genes referred to as the candidate gene approach.

DNA Markers

Markers can be used to localize genes responsible for qualitative traits like coat colour (e.g. Johansson Moller et al, 1996), and they can also be used to detect genes with substantial effects on quantitative traits like growth rate, IMF etc. In this case the approach is referred to as QTL (Quantitative Trait Locus) mapping.

In pigs, the QTL mapping approach normally uses families created from crosses based on divergent lines e.g. Large White with wild boar or Chinese Meishan. Indeed, this approach has been used in relation to intramuscular fat (IMF). Having identified a major gene for IMF using segregation analysis (Janss et al, 1994, 1997), this group went on to QTL mapping, using microsatellite markers. They recently reported evidence for suggestive linkages with markers on chromosome 1 and a marker on chromosome 3 (De Koning et al, 1998). The same region on chromosome 1 was also identified as containing a QTL for backfat. It is not clear, however, why using this approach they were not able to find what appears to be a major gene from the segregation analysis. This example illustrates some of the difficulties with the QTL mapping approach.

A number of pig populations are now being used or have been created for the purposes of searching for meat quality QTLs. These include the following:

- Wild Boar x Large White at the Swedish University of Agriculture Sciences (Anderssson et al, 1994);
- Meishan x Large White at INRA in France, Wageningen University in the Netherlands, the Roslin Institute in the UK (Archibald et al, 1996) and at the University of Illinois (Schook and Wheeler, 1994; White et al, 1998);
- Wild Boar, Pietrain and Meishan 2-way crosses at the University of Hohenhein in Germany (Moser et al, 1998);
- Pietrain x Large White, as part of an experiment to introgress the wild type CRC1 (halothane N) allele into Pietrain in Belgium (Hanset et al, 1995a,b and Georges, pers. comm.);
- Iberian pig x Landrace in Spain (The IBMAP consortium, 1998);
- Duroc x white Miniature Breed, involving groups in Berlin, Dummerstorf and Bonn (Hardge, 1996 and pers. comm.);
- Mangalitsa x Pietrain at the Technical University of Munich (Fries, pers. comm.);
- Berkshire x Yorkshire (Large White) at Iowa State University (Rothschild, pers. comm.).

Many different traits are measured. These include carcass composition, fat and lean distribution as well as meat quality measures such as waterbinding, shear force and intramuscular fat content and taste panel assessment. Some of the first results were published by Andersson-Eklund et al (1998) from the Wild Boar x Large White population. Whilst for meat quality they did not find any QTL which reached the genome-wide significance threshold, significant QTLs for carcass characteristics, such as Loin Eye Area and Lean meat %,

were detected. The largest QTL was on chromosome 4 and is likely to be a pleiotropic effect of the previously reported QTL for backfat and growth (Andersson et al, 1994).

Although there have been successes in identifying QTL, for example for backfat on chromosome 4 and for fat androstenone level on chromosome 7 (Milan et al, 1998), it is not trivial to make use of the results within commercial breeding programmes. Many workers in this field conclude that it is necessary to identify the gene or genes underlying the QTL. This is a substantial task, as the QTL region is usually relatively large and may contain many genes. Identification of the relevant genes thus remains a significant hurdle in farm animals, although the development of improved comparative maps will allow better use of information from "gene-rich" species such as mouse and human. In the short term projects are underway to determine how such initial QTL findings can be used in commercial populations. For example, the EC Biotechnology Project entitled "Transferring QTL technology to the pig breeding industry (PigQTech)-a demonstration project", coordinated by Leif Andersson at the Swedish University of Agricultural Sciences, aims to produce a route map to assist animal breeders to exploit genome mapping information. The project involves SCAN Genetics (Sweden), a Spanish breeder, Copaga and PIC as well as the Roslin Institute, Centre UdL-IRTA and the University of Barcelona.

An alternative to the above approach would be to use markers to introgress favourable QTLs identified in a non-commercial genotype (such as the wild boar) into a commercial line (Visscher et al 1996). In this respect, it is interesting to note the recent findings from several of the PiGMaP groups with respect to backfat QTL. They have identified a QTL on chromosome 7 where the "lean" allele is contributed by the Meishan and the "fat" allele is from the Large White component of the cross (Moser et al, 1998, Milan et al, 1998, Haley, pers. comm., and Rothschild, pers. comm.). This type of effect has been found in plant species and is a potentially useful finding as we think of how to use these new tools to manipulate meat quality.

Candidate Genes

The candidate gene approach can be relatively straightforward compared to the QTL approach. For example, we have used polymorphisms in candidate genes to look for associations across populations. When associations are identified the resulting marker can potentially be used directly in breeding programmes. This approach has been used very successfully for ESR and litter size (Short et al, 1997).

An example for a candidate gene for meat quality is provided by the gene for heart fatty acid binding protein (H-FABP). Gerbens et al (1997) identified polymorphisms in this gene and found these to be associated with variation in IMF in the Duroc (Gerbens, 1998). H-FABP maps to pig chromosome 6 and not to the QTL regions identified by De Koning et al (1998), (see the section on Major Genes). A comparison of the homozygous haploid classes found that they differed by about 15% of the mean value. Interestingly the difference in IMF content is only partially explained by backfat content. The authors comment that although selection for increased IMF based on H-FABP genotype will also increase backfat, this will be countered by ongoing phenotypic backfat selection. It will be interesting to see how effective and practical this test will be in the near future. It is our understanding that the Dutch consortium who funded the work are to make the test available through license arrangements (Merks, pers. comm.).

Another relevant candidate gene approach is the research on calpain and calpastatin. In beef and sheep, there are many reports of the role of the calpain system, a set of calcium dependent proteases and their inhibitor calpastatin, both *in vivo* and post-mortem in protein turnover. See, for example, the excellent review of Koohmaraie (1996). Interestingly, Ernst et al (1997) have reported the identification of three polymorphic sites in the pig calpastatin gene.

Other markers which have been generated for meat quality based on the candidate gene approach include myogenin (increased muscle fibre number, which may impact overall pork quality) (Soumillion et al, 1997) and the dominant KIT gene leading to white coat colour in pigs (Johansson Moller et al, 1996).

A shortcoming of the candidate gene approach can be that the number of candidates is increasing substantially as more and more genes are being identified. For example, in Hwang et al (1997) at least 30 genes affecting fat tissue development are described.

DISCUSSION

Exploitation of major genes for meat quality

Improving meat quality is not just about changing levels of traits like tenderness or marbling, but it is also about increasing uniformity. The existence of major genes provides excellent opportunities for improving meat quality, since it allows large steps

to be made in the desired direction (e.g. improving technological yield of ham process by selecting against RN^- gene in pigs). Secondly, it will help to reduce variation, since we can fix relevant genes in our products. Another aspect is that major genes allow differentiation for specific markets. For example, in certain types of dry cured ham a high IMF is required, whereas other products like cooked ham require a low amount of IMF. For the future it is expected that processors and retailers will specify a whole series of genes that have to be present or absent for each product that they process or sell.

Some of the major genes can be fixed or eliminated just by using phenotypic data. These data can be derived in simple or more complicated ways, e.g. like the RN gene through biopsis. For other genes, it will be essential to use molecular genetic technology. The elimination of HAL-carriers is a good example of this requirement, as full HAL elimination was previously only possible by using expensive progeny testing. The other advantage of the DNA technology is that markers close to relevant genes or tests that identify mutations in candidate genes allow us to also exploit genes with smaller effects (e.g. H-FABP gene for IMF).

For a proper exploitation of major genes it is critically important to know what type of meat we want to select for. This is not a trivial issue, as meat is processed and used in many different ways. One possible solution is that breeding companies need to be able to provide choice. The HAL gene can be used as a nice example. Some breeding organisations provide HAL-negative Pietrain boars, next to HAL-positive boars. Breeding organisations can provide such a choice in two ways: (1) fixing the gene in one base line and eliminating the gene in another line, and (2) maintaining segregation of the gene and performing DNA tests on the potential breeding animals that are used at commercial level. In the first option there are high initial costs for DNA tests but thereafter the only extra costs are the maintenance and improvement of multiple lines within a breed. In the second option there are no costs of maintaining multiple lines but DNA tests have to be performed continuously on potential breeding animals.

Potential of DNA marker assisted selection

Information at DNA level can help to fix a specific major gene, but it can also assist the selection of a quantitative trait for which we already select. Molecular information in addition to phenotypic data can increase the accuracy of selection and therefore the selection response. The size of the extra response in such a Marker Assisted Selection (MAS) scheme has been considered by many workers from a theoretical point of view. In general terms, MAS is more beneficial for traits with a low heritability and which are expensive to measure phenotypically. The results obtained depend, of course, very much on the assumptions made in the models. Gibson (1994) and others have shown that there is a short term benefit in using MAS, but that in some cases this can lead to a long term penalty. However, this is over a relatively long time frame. More recently Meuwissen and Goddard (1996) considered a different set of assumptions and in particular looked at the impact for traits such as reproduction and meat quality that are difficult to progress using traditional methods. Their results are extremely encouraging, showing that for traits such as meat quality, where the trait is measured after slaughter, an additional response of up to 64% could be achieved. Importantly, they also pointed out that this type of response could be sustained if new markers could be continually identified. For example, new markers would be added to the selection index as old markers begin to reach fixation.

In the meantime we anticipate that significant progress will be made by utilising candidate genes and searching for population wide linkage disequilibrium, using tools such as AFLP. This technology is an extremely powerful tool for revealing useful polymorphisms in commercial populations. For example, we have used AFLP and bulk segregant analysis to find markers for coat colour (Plastow et al, 1998) which are useful for ensuring white skin for slaughter pigs in markets such as the UK and Italy. We believe that this approach is applicable for other traits, an example of its application would be the generation of simple markers for QTL identified using microsatellite based QTL mapping. Such markers would then enable use without the need for family information as was the case originally for coat colour and RN^-.

Work is also underway in other species, particularly, sheep, deer and beef cattle. Taylor and Davis (1997) have recently reviewed the prospects for beef cattle, and this provides a good indication of what might be achievable. They indicate that projects are underway to identify QTLs affecting growth and carcass attributes of beef cattle in Australia, Japan and Belgium as well as in the US (MARC and Texas A&M). The first results of the Texas A&M group indicate that QTLs were detected for nearly all of the traits examined. In particular, they report a QTL influencing the proportion of unsaturated and saturated fatty acids in adipose tissues, four QTLs that appear to influence marbling and another four that influence measures of tenderness.

Practical implementation of selection for meat quality

As stated earlier, the best approach to genetically improve meat quality is to find relevant DNA-markers directly in the populations under selection. For this reason, meat quality measurements should be performed continuously on the nucleus populations of breeding organizations. Since a full assessment of meat quality can only be done after slaughter, the data have to be collected on culled animals and cannot be obtained on potential breeding animals.

The phenotypic meat quality data will not only enable the detection of relevant DNA markers, but will also be used to validate markers from experimental populations or to test candidate genes. Significant markers or genes will be included straight away in the selection process. An advantage of the molecular information is that we can obtain it already at very young age, which means that animals can be preselected based on DNA markers before the growing performance test. This is a great advantage for the overall testing and selection system.

The continuous collection of meat quality data from nucleus lines is expensive. However, its use is not limited to DNA marker research. The data also allow the breeding organization to monitor their nucleus lines, which is important for optimizing the breeding direction. Furthermore, the data can be used directly in the selection process as phenotypic information on relatives (culled litter mates and half-sibs) of potential breeding animals.

Future research

The Halothane gene has shown us that the effects of a major gene can be very dependent on the environmental conditions, which is referred to as Genotype x Environment (G x E) interaction. Moreover, a major gene may have interactions with other genes (G x G). These G x E and G x G interactions may explain the variable results that can be found in the literature on a major gene like Halothane, since different research groups use different slaughter techniques and different breeds. We need to get a better understanding of these interactions, and this is likely to be achieved through more fundamental research.

More research should also be conducted on the specific requirements of the meat for various applications. At the moment, it is very difficult to quantify the value of certain meat quality attributes to the pork chain. As a result, there may be not enough incentive for breeders to select for meat quality, or breeders may find it difficult to make a choice on the direction of selection for certain traits.

Meat scientists investigating the effects of slaughter and processing conditions, should be aware of the large effects genetic variability can have on their experiments. They should always store DNA friendly samples of the experimental animals for direct or future genotyping. Standardization or correction for genotype will increase the power of experiments.We may speculate that future meat research will be done mainly with fully identical individuals of cloned lines.

For fundamental research on gene effects on meat quality, genetically modified animals are likely to be used as research models. At the moment, this can be done already with laboratory animals, eg. the extremely muscular mouse resulting from a knockout deletion of the myostatin gene (McPherron et al, 1997), but in the future this may well be done directly with farm animals.

CONCLUSIONS

- Major genes and DNA technology provide excellent opportunities to improve meat quality in selection schemes
- Selection on major genes will not only increase average levels of quality but also decrease variability (ie increase uniformity). On the other hand, major genes can be exploited for differentiation for specific markets.
- DNA studies on candidate genes have already provided useful tools for selection for meat quality, and this situation will continue. QTL mapping has had limited application so far, but is expected to make a bigger contribution in the future.
- Phenotypic meat quality data on culled nucleus animals provide an important basis for the development and validation of DNA tests for meat quality.
- More fundamental research is necessary to understand the interactions of genes with each other and with environmental factors
- Future meat research on effects of non-genetic factors will be done with more standardised genotypes to increase experimental power. Research on genetic factors may involve genetically modified animals.

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