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Application of genomics to the pork industry[1]

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ABSTRACT: A relatively small number (less than 100) of DNA markers have been applied in swine breeding up to this point in time. Even so, these markers have been used for a range of different traits. Markers explaining variation in growth, lean percent, litter size, meat quality, susceptibility to developmental abnormalities, and even disease resistance have been identified and incorporated into breeding programs. Importantly, genomic and statistical tools have been developed to make use of the proliferation of genomic information that is now available. The ability to efficiently combine this information with quantitative genetics is the key to delivering continuing value for the swine industry. These DNA markers are analogous to a "turbocharger"—they work best with a good engine and chassis.

Key Words: Genomics, Growth, Health, Meat Quality, Pigs

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Introduction

Genetic improvement has, until very recently, been based on the "infinitesimal model," which simply treats the genotype as a "black box" consisting of a very large number of genes, each of very small effect. This theory has been successfully implemented by animal breeders for many species, especially in the last 50 yr for cattle, pigs, and poultry. Milk yield and the cost of lean meat (from the input and output point of view) have changed remarkably as a result of these efforts (see Table 1). These changes are the result of genetic improvements combined with changing production systems. In particular, highly heritable traits, such as milk production in dairy cows and lean percentage in pigs and broilers, are predominantly improved through the genetic route. We now know that there is a finite number of genes (approximately 30,000 for pigs, a number though that is still very large and would justify the infinitesimal model). However, we also know that variation in some genes (or other sequences) can have a very large effect, with the "halothane gene" being the first example of a so-called major gene in pigs. But importantly, gene variants can make a significant contribution to quantitative variation, and these gene variants (alleles) can be identified and used within the genetic improvement program (see Table 2). The genotype at each of these loci provides information that can be incorporated into the genetic models to increase accuracy of estimated breeding values and the rate of genetic improvement, and possibly to more directly exploit the underlying biological effects involved.

Animal breeders are interested in the association between alleles and traits of interest. The first step (Phase 1) in the process has been the definition of candidate genes, either directly or as "positional candidates" given results from QTL mapping studies. These genes are identified based on knowledge of gene function and expression and also ideally the position within the genome (e.g., in relation to the results of QTL studies). The increasing knowledge of the genome (from gene sequence or from expression studies) makes it possible to work on large numbers of candidate genes ("Phase 2"). This is based on the efficient identification of polymorphisms within populations for these genes and the study of associations between these polymorphisms (e.g., SNP) and traits of interest. For efficient implementation, this analysis should also consider an association with indirect or secondary traits, so that the real economic value of a marker can be established. It should be clear then, that both effective research and effective application are dependent on a program that integrates pedigree and phenotypic data collection with the genomics effort. For example, in the Pig Improvement Co. (**PIC**; Franklin, KY), genetic improvement is driven

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Table 1. Improvement of performance in livestock species from the 1960s to the present

Species	Trait	Performance[a]		
		1960s	Present	% change
Pigs	Pigs weaned/(sow·yr)	14	21	50
	Lean, %	40	55	37
	Feed conversion ratio (FCR)	3.0	2.2	27
	Lean meat, kg/t of feed	85	170	100
Broilers	Days to 2 kg	100	40	60
	Breast meat %	12	20	67
	FCR	3.0	1.7	43
Layers	Eggs/yr	230	300	30
	Eggs/t of feed	5,000	9,000	80
Dairy	Milk production/(cows·lactation), kg	6,000	10,000	67
Average		—	—	>50

[a]The figures vary greatly between regions and production systems, and the table provides an indication of the change, rather than accurate estimates.

from a relational database containing pedigree-linked animals and their data (phenotypic, quantitative, DNA marker genotypes, and even functional genomics information) from farms across the world (more than 5 million animals will have been incorporated by 2004). This required the development of a suite of software tools that extract the maximum amount of information for each task (marker association analysis or the calculation of increasingly accurate estimates of breeding values expressed at the commercial level).

Genomic results can be applied in three ways: more rapid accurate baseline improvement, commercial product differentiation, and new data to drive further research. This article will provide examples of applications for different traits and illustrate how the development of large numbers of markers across the genome (Phase 3) and functional genomics will provide new tools to affect traits that have been refractive to improvement by traditional methods.

Results

Phase 1

Genes within the leptin pathway represent candidate genes for traits such as feed intake, growth, and fatness. A DNA SNP was identified in the *MC4R* gene of pigs and found to explain variation in production traits in several breeding lines (Kim et al., 2000). The polymorphism resulted in a change in an AA in a highly conserved region of the protein, suggesting that the change was causative. However, initially, the effect within one of the populations tested (a Meishan synthetic line) was not significant, and the small effect for backfat observed with this population was in a direction opposite to that reported in the other lines. Even so, analysis of a larger dataset that took into account the potential for stratification within the populations seemed to confirm that the polymorphism was either causal or in very strong linkage disequilibrium with the causal mutation (Hernandez-Sanchez et al., 2003). Subsequently, similar results were obtained for the Meishan synthetic population, when additional data were added to the analysis, as those reported for the other breeding lines (Wilson et al., 2004). For example, the average difference between the homozygote genotype classes for days to 110 kg for the four pure lines reported in Kim et al. (2000) was 3.3 d, and it was 1.6 d for the Meishan synthetic line (Wilson et al., 2004). These results illustrate the importance of adequate sample size and also take into account potential admixture within populations when analyzing for marker effects. More recently, Kim et al. (2004b) presented results demonstrating that the original mutation may be causative by showing that the different *MC4R* alleles differ in their response to ligand binding using an in vitro gene expression system. Cells expressing both variants behaved very similarly in terms of ligand binding and cell surface expression; however, the Asn298 variant did not result in any increase in adenosine 3′,5′-cyclic phosphate content after binding of the ligand. Thus, it was concluded that this unconserved variant does not activate adenylyl cyclase. It is not surprising, therefore, that very consistent results have been obtained with this DNA marker in commercial crossbred genotypes as well as breeding lines. For example, Jungst et al. (2001) found additive effects of 0.07 kg/d for feed intake ($P < 0.05$) and 0.6 mm for backfat thickness ($P < 0.05$), and extended the findings to show improvements in loin depth (0.7 mm; $P < 0.10$) and primal yield (e.g., AutoFOM [SFK Technology A/S, Herlev, Denmark] ham, 0.11 kg, $P < 0.05$; and AutoFOM loin, 0.09 kg, $P < 0.05$) for the more efficient genotype. Similar results were obtained in the United Kingdom when boars were selected using *MC4R* genotype. In this case, offspring (several thousand) from boars of the "lean" genotype (associated with slower growth, lower feed intake and lower backfat) had approximately 1.5 mm less P2 backfat ($P < 0.001$) and 0.6% more lean in the carcass ($P < 0.001$; reported in Plastow, 2003b). More importantly, the frequency of the polymorphism is at an intermediate level in a number of breeding lines, so that the marker can be used effectively in

Table 2. Examples of marker application in the pork industry[a]

DNA marker/Gene	Developer	Trait	First application	Reference
HAL1843 (*CRC1*)	Guelph/Toronto	Stress susceptibility; MQ; Yield/FC	1991	Fujii et al., 1991
ESR	ISU/PIC	LS	1994	Rothschild et al., 1996; Short et al., 1997
cKIT	Uppsala/PIC	Dominant white; Dam line development	1996	Johansson Moller et al., 1996; Marklund et al., 1998; Giuffra et al., 2002
MC4R	ISU/PIC	DG/FC/Lean	1998	Kim et al., 2000
FUT1	NADC/ETH	DR	1999	Meijerink et al., 2000
RN^-/rn+ (*PRKAG3*)	INRA/Uppsala/Kiel; ISU/PIC	MQ	1997/1999/2000	de Vries et al., 1997; Milan et al., 2000; Ciobanu et al., 2001
IGF2	Liege/Uppsala	Lean	2002?	Jeon et al., 1999; Nezer et al., 1999; van Laere et al., 2003
MQ (several genes)	PIC and PIC/ISU	MQ	2001	Knap et al., 2002
CAST	ISU/PIC	MQ	2003	Ciobanu et al., 2002, 2004
RL, DA	PIC	RL, DA	2003	Plastow et al., 2003

[a]MQ = meat quality; FC = feed conversion; LS = litter size; DG = daily gain; RL = reproductive longevity; DA = developmental abnormality (e.g., susceptibility to hernia). ISU = Iowa State University; NADC = National Animal Disease Center, Ames, IA; ETH = Swiss Federal Institute of Technology, Zurich, Switzerland; INRA = Institut National de la Recherche Agronomique, France.

selection for these traits. This illustrates how even a marker explaining a relatively small amount of the total variation (approximately 2 to 7% of the genetic variance according to the trait) can be used to select for products that perform significantly better at the commercial level. The effect is a combination of the size of the effect and the allele frequency in the populations of interest. For example, if the frequency of a preferred allele is close to fixation (>0.9) then the effect of selection for this allele in a population will be relatively small, whereas if it is at a low frequency then the potential for improvement is correspondingly greater.

As one would expect, the studies of obesity in mouse and man have generated a large number of potential candidate genes (*MC4R* is an example) that can be investigated for effects on growth-related traits in pigs (Kim et al., 2004c). For example, polymorphisms in *HMGA1*, a gene involved in adipocyte cell growth and differentiation, were found to be associated with variation in backfat in several different populations of pigs (Kim et al., 2004c). A similar size of effect was observed as for *MC4R*, of approximately 0.9mm between the homozygous genotypes. Interestingly, there was no evidence of an interaction ($P = 0.74$) between the two genes, *HMGA1* and *MC4R*, and the combined effect was approximately 1.9 mm between the extreme genotype classes (this is not always the case for all gene pairs; e.g., see Carlborg and Haley, 2004). In addition, important results have been obtained from QTL studies including the identification of variants at a paternally imprinted locus, *IGF2*, (Jeon et al., 1999; Nezer et al., 1999; Buys, 2003; van Laere et al., 2003) that explains variation in backfat thickness and muscle mass (in this case there is no influence on growth). Furthermore, the comparative approach has led to the identification of polar overdominance in pigs, similar to the "callipyge" effect observed in sheep but for fatness at one locus and loin eye area at a second locus (Kim et al., 2004a). These effects are of interest because of their non-Mendelian inheritance. For example, only the *IGF2* allele inherited from the sire is expressed so that offspring of boars homozygous for the favorable allele of *IGF2* are more muscled independent of the genotype of the dam at this locus. However, the favorable allele is at a relatively high frequency in commercial lines selected for leanness (Buys, 2003). The PIC and its collaborators have generated a panel of performance trait markers that are available for incorporation in the breeding program increasing the accuracy of calculation of estimated breeding values for these traits.

One of the most important areas of potential for the application of genomics is in breeding animals that are less susceptible to disease (Plastow, 2003a). This potential is well illustrated with the results obtained with the *FUT1* gene (Frydendahl et al., 2003). A polymorphism in this gene determines the susceptibility of pigs to *Escherichia coli* F18 (Meijerink et al. 2000), which causes scours and bowel edema disease in weaned piglets. Mortality can be up to 40% in naïve herds exposed to the pathogen. However, animals homozygous for the (recessive) resistant allele are completely resistant to infection by *E. coli* F18. Not only is mortality due to *E. coli* F18 decreased to zero, but the growth of the pigs is significantly higher than the surviving pigs of the susceptible genotype. In commercial trials, the difference in growth rate between the resistant and susceptible pigs surviving challenge was 0.07 kg/d ($P < 0.001$; M. A. Mellencamp, D. Sullivan, and S. B. Jungst, unpublished results). The *FUT1* marker is a useful example of using a marker for product differentiation and solution of a customer problem. In 1999, PIC started a program called "EdemaGard" and began to deliver to

customers' grandparent dam-line boars and gilts, selected for the resistant allele of *FUT1* from among its regular dam-line populations. Parent gilts produced from these grandparents are resistant to *E. coli* F18. Simultaneously, parent boars, selected for the resistant allele from within PIC's leading sire line were delivered to the same customers. This process has meant that the proportion of homozygous resistant pigs flowing through the system has increased from 8% to its current level of 35%. More than five million commercial pigs with added resistance have now been produced. Customers who are reaching these levels are experimenting with removing vaccinations and feed additives, coming to rely solely on the genetic protection afforded by these homozygous resistant animals. In November 2001, Vansickle (2001) reported on one customer's experience with the EdemaGard program in an article entitled "Genetically resistant line stops *E. coli* cold."

The selection of animals with improved meat quality is another area where marker assisted selection can have a significant impact (see Meuwissen and Goddard [1996] for a comparison of the potential effect of markers on different types of trait). The first marker to be used in pig breeding, Hal1843, had an effect on meat quality, as the mutant allele was associated with PSE meat as well as porcine stress syndrome (Fujii et al., 1991). In this case, once the mutant allele was identified, it became an industry requirement to prohibit the allele as the pork industry treated the "gene" as a defect. Therefore, although the development of the DNA marker test added millions of dollars to the pork industry, in terms of value for breeding companies and producers, the effect was probably close to zero (this aspect of value is discussed in more detail in Plastow, 2004). A similar situation existed for the RN^- mutation, another major gene that has a large effect on cooked ham yield. However, marker assisted selection allowed PIC to begin to select more effectively against the unfavorable allele in its Hampshire populations (de Vries et al., 1997), whereas other companies or countries simply terminated their Hampshire programs. Ultimately, the causative mutation was identified and the industry was able to remove the RN^- mutation from remaining Hampshire lines (Milan et al., 2000). Pig breeding companies are now paying more attention to meat quality and are including quality traits as an integral part of selection programs to make simultaneous improvements in both quality and production traits (see de Vries et al., 1998; Knap et al., 2002). The development of the field of genomics has stimulated interest in breeding for meat quality and, as was mentioned above, this "trait" constitutes a classic case in which DNA marker-based selection is at its most efficient: where the trait cannot be measured on the selection candidate but instead needs to be measured at high costs on its relatives postmortem. Once a DNA marker has been shown to be associated with variation in the target trait, then it can be used to genetically type young animals for preselection before performance testing. This is a distinct advantage over sib slaughter schemes, which are increasingly difficult and expensive to implement (Knap et al., 2002). Sib slaughter schemes, however, will continue to be used and they will be important to identify new markers and for monitoring breeding lines in order to optimize the breeding direction. The advantage of incorporating markers into selection programs can then be sustained when new markers are identified to replace older markers that begin to reach fixation. The database builds up over time to provide a very useful resource for this purpose or further validation of DNA markers identified in experimental populations or to test candidate genes (e.g., in Phase 3 of marker development; see below). Recent examples of meat quality (**MQ**) marker effects include polymorphism in the genes for calpastatin (*CAST*) and *PRKAG3* that are associated with quantitative variation in tenderness (*CAST*) and pH and color (*PRKAG3*) (Ciobanu et al., 2001, 2002, 2004). As with performance traits, PIC uses a panel of DNA markers for meat quality in its selection programs (see Table 1 in Knap et al., 2002). Again, as was the case for *MC4R*, these effects have been clearly demonstrated in commercial genotypes and commercial environments. For example, the amount of product that fails to meet specification for the Japanese market (high ultimate pH, low color) was decreased from approximately 14% to approximately 7% when a polymorphism in *PRKAG3* (Ciobanu et al., 2001) was fixed in the slaughter generation in a trial undertaken in a commercial plant with nearly 1,500 pigs (A. Sosnicki, J. Bastiaansen, and G. Plastow, unpublished results).

Phase 2

Functional genomics (e.g., transcriptomics, proteomics) offers another exciting route to finding and understanding the genes and pathways involved in processes of economic importance. These techniques and the tools that they provide allow for the identification of new candidate genes and potential DNA markers, but also the ability to study the interaction between genotype and environment. For example, an understanding of the basis of the resistance to *E. coli* F18 (a mutation in the gene, *FUT1*, encoding the enzyme α(1,2)fucosyltransferase; see above) indicates why all young pigs (before weaning) are phenotypically resistant: The gene is not expressed until after weaning. Significant functional genomics studies are now underway in the areas of disease susceptibility (e.g., for *Haemophilus parasuis*, Galina et al., 2002; Oliveira et al., 2003; www.pathochip.com; and for Porcine Reproductive Respiratory Syndrome virus (PRRSv)) and muscle/meat quality (e.g., Maltin and Plastow, 2004; Plastow et al., 2005; www.qualityporkgenes.com). Blanco and coworkers (I. Blanco, A. Canals, G. Evans, M. Mellencamp, N. Deeb, L. Wang, and L. Galina-Pantoja, unpublished results) found a genetic influence on the progression of *H. parasuis* infection in well-controlled challenge experiments. Tissue samples were collected from sites typically af-

fected by *H. parasuis* infection for RNA preparation and analysis of gene expression. Animals were characterized according to their response to challenge and "resistant" or "susceptible" groups of animals compared with controls using microarrays fabricated with cDNA libraries generated from "defense" tissues of control and infected animals. Both known and unknown genes were identified as significantly up- or downregulated in treatment vs. control samples. The known genes identified are involved in signal transduction, protein biosynthesis, trafficking and turnover, transcriptional control, immune or inflammatory response, and cell cycle control (L. Galina-Pantoja, G. Evans, S. Dornan, C. Sargent, A. Canals, and J. Ullrich, unpublished results). These identities are encouraging, and the next step is to identify SNP within some of these genes for association analysis. This may lead to the identification of DNA markers that explain variation in susceptibility to *H. parasuis* and, in some cases, general resistance to disease, thereby providing new tools to select for healthier animals. The Quality Pork Genes project was created to identify genes associated with variation in different aspects of muscle quality and then to develop genetic tools that could be used to improve the quality of pork and processed pork products. The phenotypic database (on 500 animals and more than 400 traits) is complete; cDNA microarrays have been produced and gene expression and proteomic analysis is underway to search for genes explaining variation in water-holding capacity, i.m. fat content, and tenderness (Plastow et al., 2005). The database, project samples, and resources provide the opportunity to investigate a range of growth and quality traits. Those genes (or the pathways containing such genes) where variation in expression is associated with variation in the traits of interest will become candidates for SNP identification and association analysis. Ultimately, new markers will be generated and utilized in improvement programs or to provide product differentiation, as has already been achieved in Phase 1 (Knap et al., 2002; Ciobanu et al., 2001, 2004).

The candidate gene approach clearly works as illustrated by the examples provided above. The success of this approach is based on the choice of the candidate genes, the quality of the data/DNA set and the willingness and ability to persevere, as success is not guaranteed for each project. The markers are based on causative mutations (Hal1843) or are likely to be causative mutations (e.g., *MC4R, IGF2, FUT1, PRKAG3*) or are closely linked markers (*ESR* or the first markers used to manage RN^-) or less closely linked markers (most markers).

Moving to Phase 3

The molecular tools that are now available make it possible to work on a relatively large number of candidate genes. This facilitates the development of several markers for each trait and line/breed of interest. Results of a multiple marker project are presented in Figure 1. The project involved multiple markers, traits, and lines, resulting in 4,500 estimates of a marker effect for a trait-line combination. Each result is characterized by the estimated size of the marker effect expressed in phenotypic standard deviation units (y-axis) and the significance of the effect, the *P*-value (x-axis). In general, significance increases as the size of the effect increases (as expected). The deviations of this general pattern are due to factors such as allele frequencies and sample size. The question is which results to take seriously. By taking a certain cut-off point for size of the effect and significance, we get results (Sector 1 of Figure 1) that are worthwhile to pursue. If this is set too liberally (Sector 1 is large), then too many false positive results are generated and resources are wasted in follow-up research. If, however, the cut-off-point is too restrictive (Sector 1 is small), then a large number of false negatives are generated and effects that are real are ignored. Clearly, there needs to be a balance between risk and resources. The multiple marker approach is still in development with many unanswered questions relating to interpretation of results, optimal use of resources and use of the markers in breeding programs.

The next step in this development from one to many markers is the use of thousands of markers spread over the entire genome. Meuwissen and Goddard (2000) demonstrated that taking account of linkage disequilibrium among many marker loci in a genome-wide scan could more directly relate causative mutations to the individuals that carry them. The advantage compared with linkage analysis using adjacent pedigree depends on a number of factors, including population structure and history. However, for pig population structures, exploiting linkage disequilibrium promises to increase the power to map QTL, and should lead eventually to more accurate estimates of breeding value, and/or more direct exploitation of mutation effects.

A different approach works on the hypothesis that sufficient markers can capture the entire genetic variation that exists for any heritable trait, without the need to nominate likely QTL. There may be potential to include much of the effects of both gene action and gene interaction (see Carlborg and Haley [2004] for examples and discussion of the importance of gene interaction and epistasis). This is still a very speculative concept. In theory, thousands of markers can be developed and used with a large set of phenotype data to "train" the markers to predict the breeding value of individuals. This approach can be useful in situations where trait recording is carried out intensively for a relatively short period of time, followed by a number of generations of selection on marker information (W. Muir, Genome Wide Marker Assisted Selection, Plant and Animal Genome, Poultry Workshop, San Diego CA, January 2004, personal communication). The model used, however, is much simpler than reality and the theory has not been tested with real data. The first target would be to de-

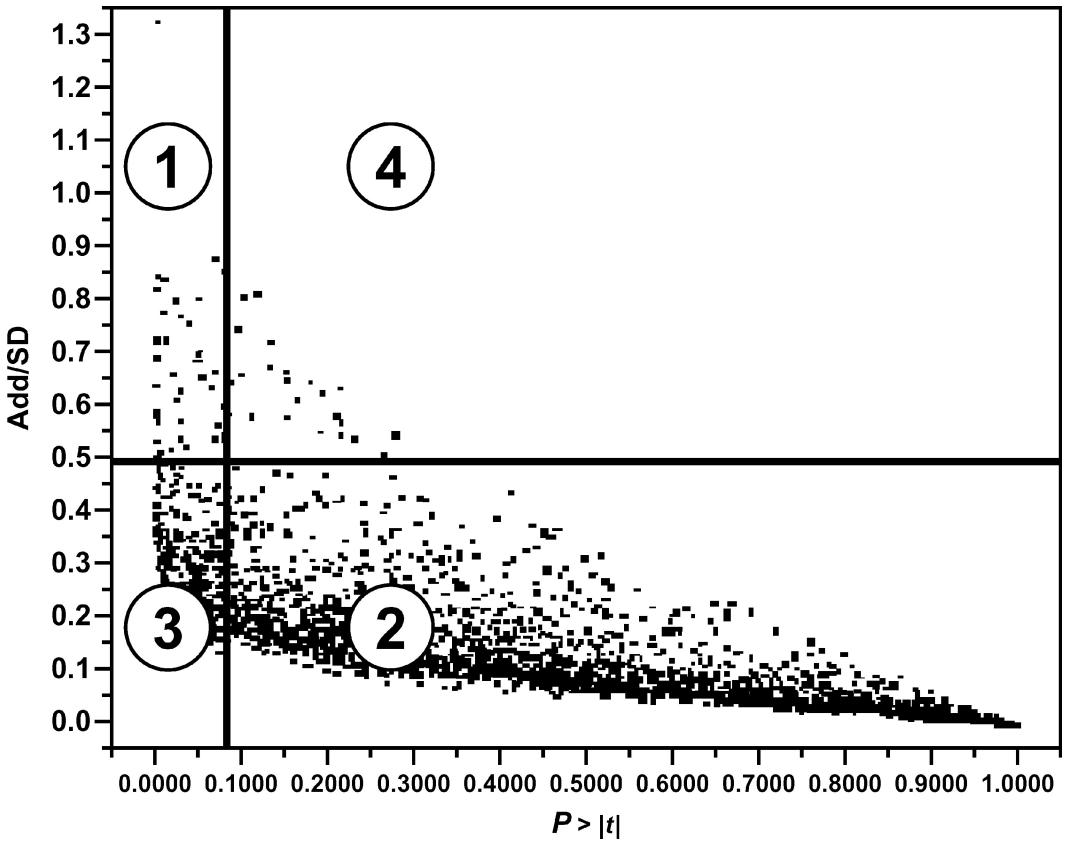

Figure 1. Results of a multiple marker project. Marker effects (Add/SD) and significance ($P > |t|$) for 4,500 estimates.

velop an advanced version of BLUP and incorporate a large number of markers in the estimation of breeding values.

Finally, genomics is contributing to the characterization of genetic diversity providing an important component for decisions on the conservation of pig breeds (Delgado et al., 2003) as well as providing tools for identity preservation or traceability. Indeed, the opportunity for genomics as well as for divergent breeds increases as greater product differentiation is required, and we should expect that it will enable the pig industry to identify and then use the gene variation that is contained within the large number of pig breeds found around the world. Both gene mapping and functional genomics may be mechanisms by which epistasis may be "tamed" for new product development. Traceability will also incorporate specific trait markers as participants in the chain as well as consumers will want confidence in the provenance of the products that they are purchasing (Delgado et al., 2003; Plastow, 2003b).

Discussion

As is illustrated previously, DNA markers are already being applied at a significant level in the swine industry today (see Table 2 for examples; we estimate that the number of markers in routine use is now more than 50). An additional example of how genomics is being used not only for product differentiation but also for ongoing product improvement programs is PIC's commercially successful 337-boar line, which sires a growing (already in double digits) share of all U.S. slaughter pigs. Its success derives from better meeting U.S. packer requirements for meat yield and pork quality, as well as producer needs for fast growth and economy. The 337 line is from a true hybrid line created by PIC, beginning in the 1970s, with at least four different breeds contributing to it at one time or another. The genotypes of a range of markers are determined early in life among all the piglets of this line. The information provided is then added into trait EBV for a more accurate estimate of breeding values and faster rates of genetic improvement of the line. However, knowledge of specific genotypes additionally allows for (and to the customer this is more immediately visible and tangible) product differentiation. One version of the 337 line is sold as a fast-growing customized line for high meat quality; it is selected with specific targets for a range of MQ markers. The line has already been developed and the resulting higher-MQ slaughter pigs from an 80,000-sow pyramid are already being harvested. Another version, on the market since 1999 and mentioned previously, is sold with homozygosity for the *FUT1* resistant allele. Yet a third version, available since 2002, is sold for cost-conscious customers who want tangibly better feed conversion. In this case, the producer not

only receives a boar with a high index value based on EBV, but specifically, the boar is homozygous for a marker that impacts appetite. It is important to note that the genomics components are added to an excellent product developed through the application of quantitative genetics. Thus, markers are analogous to a turbocharger in car production: put a turbocharger on a Pinto and you still have Pinto that cannot outrun a Corvette.

The work PIC has been conducting on meat quality since the beginning of the 1990s is already yielding outstanding products that combine fast-growing pigs that yield premium-quality carcasses at harvest. These products are already selected by incorporating DNA marker information in the improvement process. Projects such as Quality Pork Genes are beginning to add to the understanding of genes and gene interactions in growth and muscle development. This may lead to new insights that might impact human medicine as well as pork production (the identification of the RN^- is an example; Milan et al., 2000).

Implications

This review describes how the pork industry has begun to use the first results from animal genomics research. Future breeding programs will involve more traits, more data, more genetic markers, and more science. However, the key to success will remain the effective incorporation of these elements into an effective breeding program that is implemented within the genetic improvement units to deliver products that perform on farm, in the abattoir and meat chain and on to the eating experience iteself. Genomics has already been applied to influence performance at each of these steps (e.g., the effect of variation in CAST on pork tenderness), and it will be applied with increasing impact in the future. The greatest effect, however, is likely to be in developing animals that are less susceptible to disease. This is likely to require a combination of approaches and, in particular, the use of functional genomics studies to identify candidate genes along with the high-density marker approaches described as Phase 3 in this review. As with all genomics work, the most important element will be the rapid generation and utilization of the phenotypic information required to drive the discovery process. Once this information is combined with the new approaches described here, we will see applications of genomics in the hog industry on a much greater scale than are used today, helping to address the changing requirements of the different markets around the world.

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