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Mapping genes of economic importance in swine

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Introduction

Response to selection occurs through a mechanism analogous to a black box we know as the genome. Producers select the best performing animals expecting that their progeny will be superior to those produced in the previous generation without clear knowledge as to why the animals selected as parents performed at higher levels than their contemporaries. The primary goal of selection is to increase the frequency of animals with the "best" combination of alleles (forms of a gene) for each gene of economic importance.

As scientists and producers learned more about genetics, the black box has been illuminated a bit. From the rediscovery of Gregor Mendel's work to the contributions of Sewall Wright, Jay Lush, and Charles Henderson, producers now have the ability to predict the breeding value of animals with relatively high accuracy. Selection based on these procedures has been quite effective in the swine industry as evidenced by the progress made in backfat, muscling, and growth rate. Unfortunately, the genome is still a very dark shade of gray. Selection is based on the average effects of alleles an animal possesses for all genes. Selection based on the actual alleles at each gene would be a more useful tool. However, this cannot be accomplished until most of the economically important genes are discovered, and the most desirable forms (alleles) of each gene are determined. Then the genome will be illuminated, and producers can take full advantage of the genetic resources available.

How do we identify economically important genes?

Identification of a gene and its associated alleles that significantly affect performance in livestock is a monumental task. There are two approaches to accomplish the task. The first method is to test genes detected in the mapping efforts of humans and mice and hope that they will have a similar effect in livestock. However, this approach requires the information to be important in human or mice genetics and a lot of luck. Thus, most laboratories, especially those at the U.S. Meat Animal Research Center (MARC), have taken a structured approach to identify

genes which will be useful to producers. The outlined approach contains four steps, each of which is quite large, but will produce useful information.

The approach

Step 1

Identify the regions of the genome that possess genes of economic importance. This is accomplished by developing a large population of animals from a genetically diverse cross for the trait of interest, collecting phenotypic and genotypic data on all of the animals and then conducting the linkage analyses. Selection of the breeds of animals to cross is quite important. The breeds need to be as diverse for the target phenotype as possible as well as genetically distinct. These requirements are necessary to ensure the F1 progeny will be heterozygous (have two different forms) for both the genes of interest and for the genetic markers. For most traits, a population of over 500 F2 progeny needs to be developed to detect most genomic regions. To thoroughly cover the entire genome, between 150 and 200 informative genetic markers need to be genotyped across the entire population. Thus, 75,000–100,000 genotypes need to be collected. Further studies will then focus on areas of the genome identified. The information from this phase could be used for marker assisted selection in commercial herds, but preliminary background information would need to be collected prior to implementation.

Step 2

Learn as much as possible about the region identified in Step 1. This step requires collecting genotypes for additional markers in the regions with putative genes affecting the trait across the population from Step 1, as well as collecting both genotypic and phenotypic information on other populations. This will result in an improved understanding of the actual location of the gene of interest and determine if this region is responsible for variation in other swine populations. Another phase of Step 2 is to evaluate as many different phenotypes as possible. This is an important precursor to Step 3. In many cases it may be difficult to identify logical "positional candidate genes" (a gene that lies in the region of interest and whose function is known to affect the biological processes associated with the phenotype) without this background infor-

mation. Last, but not least, a thorough study of the genome maps of swine, man, and mouse for the region of interest is important. This will direct the scientist to the appropriate location of the human genome (the genome with the most information available) to select "positional candidate genes."

Step 3

Select "positional candidate genes" and test each of them in all of the populations studied. The ideal candidate gene will have logical ties to all of the phenotypes known to be affected by this location of the genome and will map to this region as well. This step may be a slow process of selecting a gene, determining if it is associated with the phenotype and, if not, proceed on to select another candidate gene. This step also requires some luck. The gene of interest must already be identified and its function known in swine or another mammalian species to be selected. Once a candidate gene has passed all of the tests conducted, then it is time to proceed on to Step 4.

Step 4

Determine the DNA sequence for each "functionally different" allele present in commercial swine. This will require sequencing the alleles of the genes in many different animals to detect unique alleles and then determining which unique alleles actually contribute to variation in the target phenotype. While the allele identification aspect of this step could be quite formidable, it may be an even larger task to determine which unique alleles improve the trait of interest.

Resources for swine mapping at MARC

The swine resource population is comprised of a five-generation crossbred population designed to identify genes affecting reproduction, growth, and carcass composition. The population started with a cross between Meishan (a Chinese breed of swine) and White composite (composite breed developed at MARC with 1/4 Chester White 1/4 Landrace 1/4 Large White and 1/4 Yorkshire) swine. Backcross animals were produced in generation 3 (n=740) followed by two generations of half-blood pigs in generations 4 (n=800) and 5 (n=250). A genetic linkage map, based on microsatellite markers, spanning virtually the entire genome and containing over 1,100 markers has been developed¹ and can be viewed at our website (<http://www.marc.usda.gov/>).

Current status of QTL mapping

Mapping genes of economic importance is still in its infancy. Numerous laboratories are in the latter stages of Step 1 and the number of published findings will rapidly increase over the next few years. To date, only a few studies conducting genomic scans for regions of the genome

containing economically important genes have been reported. Remarkably, in spite of the few studies that have been conducted through the structured approach listed above, differences in the DNA sequence for three different economically important genes have already been determined. Differences in DNA sequences which putatively cause the observed phenotypic effect have been identified for malignant hyperthermia², dominant white color³, and resistance to diarrhea caused by *E. coli* F18⁴.

Regions detected at MARC

All procedures necessary for Step 1 have been completed for carcass composition traits^{5,6}. The current emphasis is on identifying the regions of the genome that affect reproduction and many results look promising despite their preliminary status. After completion of the reproductive traits, evaluation of the growth traits will follow (weight at birth, weaning, and four week intervals until seven months of age).

Three regions were significant for many of the carcass composition traits. These regions are located on chromosomes 1, 7, and X. Each of these regions significantly affected backfat and a summation of their effects could reduce backfat in a half Meishan population by approximately 1 cm⁵. Each of these regions was also associated with two other traits analyzed⁶. The regions on chromosomes 1 and X also affected loin eye area and trimmed wholesale product yield. The region on chromosome 7 was highly significant in the analyses of dressing percentage and carcass length. There is evidence indicating that genes affecting carcass composition may also exist on chromosomes 8 and 14.

Reproduction phenotypes being analyzed include age at puberty, ovulation rate, and uterine capacity (the total number of fetuses which could be supported to term by the uterus). Preliminary results indicate that more regions will be identified affecting ovulation rate than any other phenotype studied.

Emphasis of future research at MARC

Initiation of Step 2 procedures have begun for genomic regions affecting carcass composition and some of the preliminary results for reproduction (primarily ovulation rate). While most of the data are collected to complete Step 1 for growth traits, analyses will be initiated after completion of the reproductive traits. The most time consuming phase of Step 2 is the development of new markers in specific regions of the genome. Despite the large number (over 1100) of markers currently available, additional markers are necessary to test the genomic segment in other populations of swine, particularly populations which do not contain Meishan germplasm. As less genetically diverse swine populations are studied (such as purebred or crosses between typical U.S. breeds), many

genetic markers will not be informative. So a battery of markers need to be available to determine which ones will be useful in each population. Another area of research is to map genes in the swine genome to increase the number of ties between the swine and human genomes.

Applications and implications

There are many hurdles to overcome before the findings of current genetic studies can be fully utilized. The regions identified in genomic scans by research at MARC^{5,6} or other laboratories^{7,8,9} for growth, reproduction, or carcass composition could be tested in commercial swine populations today. Unfortunately, the preliminary information would need to be gathered (at a substantial cost to the producer) and proper interpretation of the data likely requires more knowledge about genetics and statistics than most producers currently possess. There appears to be a need in the industry to reduce the cost to collect genotypic data and to have consultants available who could interpret these data.

Because of the two limitations listed above, most scientists attempt to identify the gene and its alleles that cause the differences in phenotypes. This requires much more development time and money, but when successful, the results can be easily and rapidly transferred to producers at a reasonable cost. When the functionally different alleles are identified, an easily interpretable test can be developed where allele "A" is the desirable allele and allele "B" is undesirable. An example would be the test currently available for the "stress gene" (ryanodine receptor 1).

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