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BREEDING AND GENETICS SYMPOSIUM:
Systems biology in animal breeding: Identifying relationships among markers, genes, and phenotypes[1]

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The Breeding and Genetics Symposium titled "Systems Biology in Animal Breeding: Identifying relationships among markers, genes, and phenotypes" was held at the Joint Annual Meeting of the American Society of Animal Science and the American Dairy Science Association in Phoenix, AZ, July 15–19, 2012. The primary goal of the symposium was to demonstrate the use of high-density SNP genotypes to determine the complex regulatory relationships among genotypes and phenotypes but also to present methods for studying complex relationships among phenotypes. Case studies from mammalian and avian species were included to emphasize the broad applicability of these methods.

Modern systems biology attempts to explain how variations in DNA markers relate to phenotypes through transcription, protein, and regulatory networks. Systems biology is a rapidly growing field of study, and many animal breeders are unfamiliar with this area. Still, resources for such work are rapidly becoming available, including high-density SNP genotypes for thousands of phenotyped dairy cattle collected by the North American dairy industry in the National Dairy Database maintained by the Animal Improvement Programs Laboratory (Beltsville, MD), and several multi-institutional and some international projects are genotyping and phenotyping animals for novel traits such as efficiency of production. In addition, a number of competitive grants recently awarded by the USDA National Institute of Food and Agriculture's Agriculture and Food Research Initiative competitive grants program include 1 or more objectives incorporating systems biology approaches in several species, including cattle, swine, and poultry. There is substantial evidence that most QTL in the cattle genome explain only small proportions of additive genetic variance for important phenotypes (e.g., Cole et al., 2011). Recent papers, such as Fortes et al. (2011) have shown that gene network analysis can provide powerful insight into the genetic architecture underlying complex phenotypes.

Fortes et al. (2010) presented a method that combined genomewide association analysis using SNP genotypes with gene network theory using it to dissect a complex trait, age at puberty. The symposium's first speaker, Toni Reverter (Commonwealth Scientific and Industrial Research Organisation, Brisbane, Australia), presented 2 examples of how to use that approach to identify gene networks, with particular emphasis on the use of complexes formed from the intersection of multiple networks (Reverter and Fortes, 2013). In both illustrations, the results from SNP-based association analyses were used to perform inference on gene regulatory networks. The presentation also included a demonstration of how multiple populations (e.g., breeds) can be used in a single analysis to refine gene networks to more precisely identify their critical nodes. The discussion also included details about available tools for performing such analyses.

In the second presentation, Warren Snelling (USDA-ARS U.S. Meat Animal Research Center, Clay Center, NE) accentuated some of the important points

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raised in the first presentation and emphasized the need to move beyond SNP–QTL associations based on linkage disequilibrium in favor of genetic variants that are informative across breeds (Snelling et al., 2013). Such developments are critical to use information from large populations to help improve smaller ones, such as using Holstein data to improve the accuracy of genomic breeding values in Brown Swiss or Ayrshire cattle. The real challenge to increasing SNP–QTL correlations is the current lack of knowledge of the causal variants that underlie phenotypic variation. There also was discussion of the challenges in gene network analysis related to the lack of high-quality assembly annotation and limited knowledge of gene function in the cow.

In the third talk, Guilherme Rosa (Department of Animal Sciences, University of Wisconsin, Madison) focused on methods for the inference of causal effects from field data, such as health event data from on-farm computer systems (Rosa and Valente, 2013). The principal challenge in such analyses is the distinction between correlation and causal associations. Two phenotypes may be correlated because they share a common causal factor or because one phenotype has a causal effect on the other. Tools for delineating those cases include path analysis and structural equation models, and the presenter discussed several parameterizations of structural equation models based on the assumptions that can be justified in a given analysis. The value of data captured on-farm but not currently used for genetic or management decision making also was emphasized because of the cost of developing and implementing de novo data collection schemes.

Emphasis shifted from methods to applications with the fourth talk, in which David Froman (Department of Animal and Rangeland Sciences, Oregon State University, Corvallis) described a systems biology approach to study chicken semen quality (Froman and Rhoads, 2013). The phenotype of interest in this case was sperm mobility measured in lines selected for low and high mobility. Single nucleotide polymorphisms associated with the difference between the lines have been identified, with 2 loci associated with poor sperm mobility identified on the Z chromosome. These results suggest that there is a maternally transmitted genetic element that is independent of autosomal genes influencing rooster fertility.

The symposium closed concluded with a presentation on the biology of cellular Fe regulation in bovine skeletal muscle (Koltes et al., 2012). In this presentation, the commonly used approach of combining SNP genotypes with phenotypic data was discussed, but whole transcriptome shotgun sequencing analysis of mRNA levels also was used to investigate differences in gene transcription. The results confirmed the role of *BMP6* and *SMAD1* in Fe homeostasis and also identified the *SMAD3* pathway as a potential novel regulator of Fe homeostasis.

The use of high-density SNP genotypes has improved the accuracy of genetic improvement programs in several species, but results of genomewide association studies have shown that much of the genetic variation associated with phenotypes of economic importance in livestock is not explained by SNP with large effects. The Breeding and Genetics Symposium on systems biology in animal breeding provided an overview of how systems biology tools can be used to provide a more complete view of genetic mechanisms underlying complex phenotypes.

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