INVESTIGATIONS

1881–1891 Molecular Insight into the Association Between Cartilage Regeneration and Ear Wound Healing in Genetic Mouse Models: Targeting New Genes in Regeneration
Muhammad Farooq Rai, Eric J. Schmidt, Audrey McAlinden, James M. Cheverud, and Linda J. Sandell
Although tissue regeneration in mammals is rare, some mouse strains possess the ability to heal tissues even into adulthood. These authors have previously demonstrated a negative genetic correlation between tissue healing and osteoarthritis susceptibility. In this study, they analyze knee joints from healer and non-healer strains and identified genes common to both ear wound and knee cartilage healing. Specific sequence differences between healer and non-healer parental strains were identified as potential causal polymorphisms. Mapping genetic variations that give rise to differences in diverse healing responses may reveal healing processes in pursuit of new therapeutic targets designed to regenerate tissues and offer protection from osteoarthritis.

1893–1901 Genetic Background and GxE Interactions Modulate the Penetrance of a Naturally Occurring Wing Mutation in Drosophila melanogaster
Joseph Lachance, Lawrence Jung, and John R. True
In this article, the authors examine incomplete penetrance in a classic model system (Drosophila melanogaster). Penetrance refers to the proportion of individuals with a given genetic variant that show the expected phenotype. By assessing the penetrance of wing defects, the authors determined the extent to which vesiculated mutants are buffered from alleles at other loci and environmental effects. Using the tools of classical genetics, they found significant epistasis, genotype-by-environment interactions, maternal effects, and evidence of naturally segregating suppressors.

1903–1926 Genomic Prediction in Maize Breeding Populations with Genotyping-by-Sequencing
José Crossa, Yoseph Beyene, Semagn Kassa, Paulino Pérez, John M. Hickey, Charles Chen, Gustavo de los Campos, Juan Burgueño, Vanessa S. Windhausen, Ed Buckler, Jean-Luc Jannink, Marco A. Lopez Cruz, and Raman Babu
Genotyping-by-sequencing (GBS) has become an attractive alternative technology for genomic selection. This study sought to evaluate various methods for incorporating GBS information and compare them with pedigree models for predicting lines from two maize populations. The authors incorporate GBS and pedigree data into GBLUP or RKHS regressions. Their results show consistent gains in prediction accuracy by combining pedigree and GBS data, and increased predictive ability when using imputed or non-imputed GBS data over inferred haplotype in Experiment 1, or non-imputed GBS and information-based imputed short and long haplotypes, as compared to the other methods in Experiment 2. Also, the level of prediction accuracy achieved using GBS data in Experiment 2 is comparable to the level reported by previous studies analyzing this data set using SNP arrays.
A Mutation in the FHA Domain of *Coprinus cinereus* Nbs1 Leads to Spo11-Independent Meiotic Recombination and Chromosome Segregation

K. Nicole Crown, Oleksandr P. Savytskyy, Shehr-e-Banoo Malik, John Logsdon, R. Scott Williams, John A. Tainer, and Miriam E. Zolan

For most organisms examined, Spo11-induced DNA double-strand breaks (DSBs) are required for meiotic recombination and accurate segregation of homologous chromosomes. In this study, the authors examine how mutations in Nbs1, a protein required for DSB processing, affect meiotic recombination and successful completion of meiosis. Molecular modeling showed that an amino acid substitution in Nbs1 protein made by the mutant *nbs1-2* is predicted to weaken its association with Ctp1, another meiotic protein. Recombination in *nbs1-2* utilizes Spo11-independent DSBs, likely formed during pre-meiotic DNA replication and leading to high levels of accurate chromosome segregation. This study illustrates the remarkable flexibility of the meiotic process.

Comparative Analyses Identify the Contributions of Exotic Donors to Disease Resistance in a Barley Experimental Population

Zhou Fang, Amber Eule-Nashoba, Carol Powers, Thomas Y. Kono, Shohei Takuno, Peter L. Morrell, and Kevin P. Smith

The authors report the genetic effects of introgression from a diverse set of barley lines carrying *Fusarium* head blight resistance into an existing breeding population. They demonstrate that comparative population genetic approaches applied to this experimental population provide a complementary approach to QTL and association mapping methods for identifying loci that underlie important phenotypes.

A DNA Sequence Element That Advances Replication Origin Activation Time in *Saccharomyces cerevisiae*

Thomas J. Pohl, Katherine Kolor, Walton L. Fangman, Bonita J. Brewer, and M. K. Raghuraman

Chromosome replication is initiated at specific DNA sequences known as origins of replication. Origins across the genome may differ in efficiency and time-of-activation, raising the question of how this replication program is choreographed. This study identifies and characterizes a DNA sequence in baker’s yeast that can advance the activation time of the well-studied origin ARS1 when placed in its proximity. These results further support the idea that origin activation time depends on context rather than on origin sequences themselves. They also provide another instance of a defined sequence that modulates origin activity.

Characterization and Prediction of Haploinsufficiency Using Systems-Level Gene Properties in Yeast

Matthew Norris, Simon Lovell, and Daniela Delneri

Many organisms, including humans and yeast, have two copies of each gene. Organisms may sometimes have problems when one copy of a gene is missing. When this happens, the gene is described as “haploinsufficient” (HI). In this study, the authors identify several gene properties significantly associated with HI. The authors made predicted the likelihood of each gene being HI. They tested the genes with the highest HI likelihoods using experiments to measure growth rates of strains with a missing gene copy. Six genes had significant HI, demonstrating the effectiveness of the authors’ predictions.

Mapping Condition-Dependent Regulation of Lipid Metabolism in *Saccharomyces cerevisiae*

Michael C. Jewett, Christopher T. Workman, Intawat Nookaew, Francisco A. Pizarro, Eduardo Agosin, Lars I. Hellgren, and Jens Nielsen

Elucidating global regulatory mechanisms in lipid metabolism has direct implications for human health, biotechnology, and synthetic biology. Despite these interests, comprehensive studies integrating genome-wide expression data, metabolite levels, and lipid levels are lacking. These authors mapped condition dependent regulation controlling lipid metabolism in *Saccharomyces cerevisiae*. They then developed and validated integrative methods for data analysis that use correlation analysis, metabolic topology, and transcription factor enrichment to interrogate and characterize the complex relationships that arise across multiple environmental conditions. This work will serve as a rich data resource for studying lipid metabolism and may inspire larger integrated systems biology efforts.
Cell-Type–Specific Transcriptional Profiles of the Dimorphic Pathogen *Penicillium marneffei* Reflect Distinct Reproductive, Morphological, and Environmental Demands

Shivani Pasricha, Michael Payne, David Canovas, Luke Pase, Nathamon Ngaosuwankul, Sally Beard, Alicia Oshlack, Gordon K. Smyth, Sansanee C. Chaiyaroj, Kylie J. Boyce, and Alex Andrianopoulos

*Penicillium marneffei* is an opportunistic human pathogen. The pathogenic form, produced at body temperature (37°C), grows as a unicellular yeast while the non-pathogenic multicellular hyphal form is produced at 25°C. Transition between these growth forms, known as dimorphic switching, is triggered by temperature. To gain insights into the control of dimorphic switching and the properties of the resultant cell types, the authors conducted expression profiling and identified which genes were expressed under each condition. A number of these genes were further characterized by creating and analyzing mutants. These were shown to be important for various aspects of growth.

Extension of the Caenorhabditis elegans Pharyngeal M1 Neuron Axon Is Regulated by Multiple Mechanisms

Osama Refai, Patricia Rohs, Paul E. Mains, and Jeb Gaudet

Neurons employ different mechanisms to extend axons through different environments. The growth cone lengthens the axon as it crawls along the substrate and samples its surroundings for guidance cues. The authors examine how the *C. elegans* M1 neuron extends its axon in the context of a developing organ, the pharynx. Extension occurs in two phases, the first of which is independent of genes used for growth cones and axon extension. The axon later employs these types of genes to follow along the cellular projection of a pharyngeal gland cell. Both phases are independent of major guidance systems, suggesting that M1 extension uses redundant or novel cues.

Construction of Reference Chromosome-Scale Pseudomolecules for Potato: Integrating the Potato Genome with Genetic and Physical Maps

Sanjeev Kumar Sharma, Daniel Bolser, Jan de Boer, Mads Sønderkær, Walter Amoros, Martin Federico Carbont, Juan Martin D’Ambrosio, German de la Cruz, Alex Di Genova, David S. Douches, Maria Eguituz, Xiao Guo, Frank Guzman, Christine A. Hackett, John P. Hamilton, Guangcui Li, Ying Li, Roberto Lozano, Alejandro Maass, David Marshall, Diana Martinez, Karen McLean, Nilo Mejia, Linda Milne, Susan Munive, Istvan Nagy, Olga Ponce, Manuel Ramirez, Reinhard Simon, Susan J. Thomson, Yerisf Torres, Robbie Waugh, Zhonghua Zhang, Sanwen Huang, Richard G. F. Visser, Christian W. B. Bachem, Boris Sagredo, Sergio E. Feingold, Gisella Orjeda, Richard E. Veilleux, Merideth Bonierbale, Jeanne M. E. Jacobs, Dan Milbourne, David Michael Alan Martin, and Glenn J. Bryan

This article details construction of reference chromosome-scale pseudomolecules for potato using a combination of genetic mapping and informatics approaches. The study significantly increases the overall size of the anchored and oriented fraction of the potato genome assembly published in 2011. The authors’ analysis integrates the genome with a new linkage map as well as other genetic and physical maps of potato and the closely related crop plant tomato. The pseudomolecules and their links with genetic maps complement the published potato genome sequence and provide an effective platform for its exploitation. The methods employed here will be instructive in building improved genome assemblies.

Evolution After Whole-Genome Duplication: A Network Perspective

Yun Zhu, Zhenguo Lin, and Luay Nakhleh

Gene duplication plays a central role in evolution, and has been hypothesized to be a major driver of the evolution of molecular interaction networks. In this article, the authors focus on pairs of paralogous genes that originated from a whole-genome duplication event in yeast. They use these genes and the time of emergence to investigate the evolutionary rate of protein interactions and to understand whole-genome evolution from a network perspective.
Molecular Phylogeography of a Human Autosomal Skin Color Locus Under Natural Selection
Victor A. Canfield, Arthur Berg, Steven Peckins, Steven M. Wentzel, Khai Chung Ang, Stephen Oppenheimer, and Keith C. Cheng

The derived A111T allele of the SLC24A5 gene is the largest identified contributor to skin pigmentation differences between Europeans and sub-Saharan Africans, while the surrounding genomic region shows convincing evidence of positive selection. In this study, the authors analyze relationships between haplotypes within this region and learn that chromosomes carrying A111T share a common haplotype, indicating a single origin of this variant. Two haplotypes are precursors via homologous recombination to that containing A111T. The crossover and mutation leading to the A111T haplotype most likely occurred outside Africa and after the split between the ancestors of Europeans and East Asians.

Allelic Variation in a Cellulose Synthase Gene (PtoCesA4) Associated with Growth and Wood Properties in Populus tomentosa
Qingzhang Du, Baohua Xu, Wei Pan, Chenrui Gong, Qingshi Wang, Jiaxing Tian, Bailian Li, and Deqiang Zhang

Combining linkage disequilibrium (LD)-based association analysis with traditional single-SNP linkage analysis, the authors dissect the genetic effect of a Populus tomentosa cellulose synthase gene, PtoCesA4, underlying variation of the complex traits controlling growth and lignocellulose biosynthesis. They identify three strong associations, including two non-synonymous markers (SNP49 associated with α-cellulose content and SNP59 associated with fiber width) and a noncoding marker (SNP18 associated with α-cellulose content) in an association population and a family-based linkage population simultaneously. These functional PtoCesA4 allelic variations underlying natural variation in complex quantitative traits in trees may enable marker-assisted breeding to improve wood quality and yield.

Dissecting Genome-Wide Association Signals for Loss-of-Function Phenotypes in Sorghum Flavonoid Pigmentation Traits
Geoffrey P. Morris, Davina H. Rhodes, Zachary Brenton, Punn Ramu, Vinayan Madhumal Thayil, Santosh Deshpande, C. Thomas Hash, Charlotte Acharya, Sharon E. Mitchell, Edward S. Buckler, Jianming Yu, and Stephen Kresovich

Genome-wide association mapping is a powerful tool to dissect the genetic basis of natural variation, but it remains difficult to precisely identify the underlying genes due to population structure and multiple causative factors. These authors use a classic genetic model, crop plant pigmentation, to compare the ability of several mapping strategies to precisely identify causative genes, and learn that linear modeling approaches that account for relatedness among individuals in the mapping populations sometimes fail to identify a known major-effect gene underlying sorghum grain tannins, while a simple genome scan for loss-of-function variants in fact identifies the correct gene.

A Genome-Wide Association Study Reveals Genes Associated with Fusarium Ear Rot Resistance in a Maize Core Diversity Panel
Charles T. Zila, L. Fernando Samayoa, Rogelio Santiago, Ana Butrón, and James B. Holland

Fusarium ear rot disease is common worldwide, and leads to reduced yield. The causal fungus may also contaminate corn grain with a mycotoxin hazardous to human health. Because the disease cannot be controlled with fungicide, breeding for resistance is necessary. Using extensive field phenotyping and genome-wide association analysis of a core diversity maize panel, the authors identify three SNPs associated with resistance. Two of the SNPs were inside or adjacent to genes with predicted functions that could be associated with disease resistance. Breeders may select for resistance alleles associated with these SNPs from unadapted maize for incorporation into elite breeding pools.