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INVESTIGATIONS

769–777 **Yeast Growth Plasticity Is Regulated by Environment-Specific Multi-QTL Interactions**
Aatish Bhatia, Anupama Yadav, Chenchen Zhu, Julien Gagneur, Lars M. Steinmetz, Gyan Bhanot, and Himanshu Sinha

Complex phenotypes like growth respond to environmental cues like nutrition and stress. This ability to alter phenotype in different environments is Phenotypic Plasticity. Studying regulation of this phenomenon will help understand how genes interact with environment to affect various phenotypes. Using a population derived from a cross between two genetically divergent yeast strains, we show that different genes interact to regulate plasticity of growth in different carbon sources. Our results suggest that yeast has the ability to modulate different aspects of growth independently in order to maximize its fitness across varied environments.

779–781 **Genetics and Evolution: An iOS Application To Supplement Introductory Courses in Transmission and Evolutionary Genetics**
Russell B. Myers, Brandon Millman, and Mohamed A. F. Noor

Students in college courses struggle to understand many concepts fundamental to transmission and evolutionary genetics. These students consistently ask for more demonstrations and more practice problems. With this demand in mind, the "Genetics and Evolution" (GenEvol) app was designed to provide tools allowing users to: 1) simulate genetic crosses with varying numbers of genes and patterns of inheritance, 2) simulate allele frequency changes under varying evolutionary forces, 3) quiz themselves to reinforce, 4) solve various problems common in genetics and evolution courses, and 5) generate practice problems to try on their own.

783–793 **Genome Sequence of *Saccharomyces carlsbergensis*, the World's First Pure Culture Lager Yeast**
Andrea Walther, Ana Hesselbart, and Jürgen Wendland

Lager yeast are hybrids between two closely related *Saccharomyces* species. *Saccharomyces carlsbergensis* was the first pure culture lager yeast used in industrial beer fermentations, starting in 1883. We sequenced its genome and compared it to the Weihenstephan lager yeast genome, which we resequenced. We found that *S. carlsbergensis* is essentially triploid (3n-1) whereas the Weihenstephan WS34/70 strain is tetraploid. *S. carlsbergensis* has preferentially lost large parts of the *S. cerevisiae* parental genome. Both genomes are distinguished by several independent translocations, however, they also share 3 translocations. Therefore, we propose a common origin of lager yeast strains from a single hybridization event.

795–804 **A Complex Regulatory Network Coordinating Cell Cycles During *C. elegans* Development Is Revealed by a Genome-Wide RNAi Screen**
Sarah H. Roy, David V. Tobin, Nadin Memar, Eleanor Beltz, Jenna Holmen, Joseph E. Clayton, Daniel J. Chiu, Laura D. Young, Travis H. Green, Isabella Lubin, Yuying Liu, Barbara Conradt, and R. Mako Saito

Coordinating cell divisions is important throughout the life of a multicellular organism, but especially crucial for normal development. We used a sensitive reverse-genetic screen to identify 107 genes that act in a regulatory network controlling cell cycles during *Caenorhabditis elegans* development. One of the genes, *ubc-25*, encodes a ubiquitin conjugating enzyme that appears to control cell-cycle quiescence by inhibiting cyclin E expression. Their analyses of the genes suggest the multiple pathways act redundantly to ensure strict control of cell divisions.

805–812 **A MITE Transposon Insertion Is Associated with Differential Methylation at the Maize Flowering Time QTL *Vgt1***
Sara Castelletti, Roberto Tuberosa, Massimo Pindo, and Silvio Salvi

Vgt1, a major flowering time locus in maize (*Zea mays* L.) includes an evolutionarily conserved regulatory region controlling the expression of a downstream transcription factor (*ZmRap2.7*) involved in meristem differentiation. DNA methylation was investigated at *Vgt1* by bisulfite sequencing in leaf samples of isogenic inbred lines and F_1 hybrids. High methylation and methylation spreading were observed in the early-flowering *Vgt1* allele characterized by a MITE transposon insertion. Allele-specific expression assays linked altered *ZmRap2.7* transcription with the presence of the MITE and its heavy methylation. Data on methylation levels at the orthologous locus in sorghum are also presented.

813–821 **A High-Resolution Genetic Map of Yellow Monkeyflower Identifies Chemical Defense QTLs and Recombination Rate Variation**
Liza M. Holeski, Patrick Monnahan, Boryana Koseva, Nick McCool, Richard L. Lindroth, and John K. Kelly

Capitalizing on modern sequencing technology, we construct a very dense linkage map of yellow monkeyflower, *Mimulus guttatus*. We quantify genome-wide recombination rates, identify genomic inversions, and map QTL for ecologically relevant plant defense traits. Future work will determine whether life-history and other ecologically relevant traits map to the newly-identified inversions, as well as whether individual plant defense compounds have independent genetic control.

823–828 **A Novel *HSF4* Gene Mutation Causes Autosomal-Dominant Cataracts in a Chinese Family**
Huibin Lv, Chen Huang, Jing Zhang, Ziyuan Liu, Zhike Zhang, Haining Xu, Yuchen You, Jinping Hu, Xuemin Li, and Wei Wang

Congenital cataracts are a significant cause of visual impairment or blindness in children. This study reports a novel missense mutation, c.69 GT (p. K23N), in exon 3 of the *HSF4*. This mutation was found in a twelve-member, four-generation Chinese family and was associated with bilateral congenital cataracts. Also, bioinformatics analysis indicated that p. K23N was predicted to be a disease-causing mutation. This novel mutation could enable proper genetic diagnostics and counseling in affected families and could lead to a better understanding of the structure and function of HSF4 in health and disease.

829–838 **Acquisition of a Leucine Zipper Motif as a Mechanism of Antimorphy for an Allele of the *Drosophila Hox* Gene *Sex Combs Reduced***
Lovesha Sivanantharajah and Anthony Percival-Smith

Mutant alleles that are antagonistic to the wild type allele are classified as "antimorphic". The classic mechanism for antimorphy is dominant negativity where inactive mutant protein subunits retain the capacity to form complexes with wild-type subunits, resulting in inactive protein complexes. This article proposes that the antimorphy of Scr^{14}, an allele of *Drosophila Sex combs reduced* (*Scr*), is caused by the introduction of a short leucine zipper oligomerization motif in the SCR^{14} N-terminal. This mechanism of the acquisition of an oligomerization domain is distinct from dominant negativity, which maintains oligomerization for inhibition of protein complex activity.

839–850 **Coordinated Metabolic Transitions During *Drosophila* Embryogenesis and the Onset of Aerobic Glycolysis**
Jason M. Tennessen, Nicolas M. Bertagnolli, Janelle Evans, Matt H. Sieber, James Cox, and Carl S. Thummel

Drosophila utilizes aerobic glycolysis to support the rapid growth that occurs during larval development. We use modENCODE RNA-seq data and metabolomic analysis to characterize *Drosophila* embryogenesis, spanning the onset of aerobic glycolysis. These studies show the efficient use of nutrient stores to support embryonic development, define sequential metabolic transitions during this stage, and demonstrate striking similarities between the metabolic state of fly embryos and tumor cells.

851–859 **The *de novo* Transcriptome and Its Analysis in the Worldwide Vegetable Pest, *Delia antiqua* (Diptera: Anthomyiidae)**
Yu-Juan Zhang, Youjin Hao, Fengling Si, Shuang Ren, Ganyu Hu, Li Shen, and Bin Chen

The onion maggot *Delia antiqua* is a major insect pest of cultivated vegetables, especially the onion, and a good model to investigate the molecular mechanisms of diapause. To better understand the biology and diapause mechanism of the insect pest species, the *D. antiqua* transcriptome was sequenced and analyzed. These data represent the most comprehensive transcriptomic resource currently available for *D. antiqua*, and will facilitate the study of genetics, genomics and diapause, and further pest control.

861–869 **Genomics of CpG Methylation in Developing and Developed Zebrafish**
David M. McGaughey, Hatice Ozel Abaan, Ryan M. Miller, Peter A. Kropp, and Lawrence C. Brody

DNA methylation is a dynamic process through which genomic modifications can be stably transmitted from parent to daughter cells. While a large body of work suggests that DNA methylation's primary influence is to modify gene expression through CpG methylation at promoters, these conclusions were largely drawn before the advent of high-resolution genome-wide methylation assays. We mapped methylation sites across the entire genome in a variety of zebrafish embryonic and terminal tissues. We found that methylation in the average gene is highest at the last exon and that methylation outside of promoters can predict gene expression and alternative splicing.

871–883 **Bioinformatics Analysis of Alternative Polyadenylation in Green Alga *Chlamydomonas reinhardtii* Using Transcriptome Sequences from Three Different Sequencing Platforms**
Zhixin Zhao, Xiaohui Wu, Praveen Kumar Raj Kumar, Min Dong, Guoli Ji, Qingshun Quinn Li, and Chun Liang

Alternative polyadenylation (APA) plays a crucial role in gene expression regulation in eukaryotes. Different from AAUAAA, the canonical poly(A) signal detected in human and Arabidopsis, UGUAA proves to be a critical poly(A) signal in *Chlamydomonas reinhardii*, suggesting different molecular mechanisms in polyadenylation. Using a large sequence dataset from 3 different sequencing platforms, we examined poly(A) signals and their variations among different intragenic and intergenic regions, and determined APA extent and the relationship between APA and alternative splicing (intron retention) in this algal species. Our study will facilitate understanding of the underlying biological mechanism in alternative polyadeynation.

885–890 **Impact of Genetic Background on Neonatal Lethality of *Gga2* Gene-Trap Mice**
Balraj Doray, Jennifer Govero, and Stuart Kornfeld

Mammals contain 3 homologous GGAs that function as monomeric clathrin adaptor proteins. We reported that loss of GGA1 or GGA3 in mice has minimal consequences whereas gene-trap disruption of the *Gga2* gene leads to either embryonic or neonatal lethality, depending on the gene-trap vector used. We now show that the embryonic lethality is due to a factor other than GGA2. Thus GGA2 has an essential function in the neonatal period that can′t be compensated for by GGA1 or GGA3. Importantly, the incidence of the neonatal lethality is influenced by the genetic background of the mice.

891–900 **Genetic Diversity Analysis of Highly Incomplete SNP Genotype Data with Imputations: An Empirical Assessment**
Yong-Bi Fu

This paper presents a timely investigation of the pressing issue associated with the highly incomplete genotype data currently generated from genotype-by-sequencing technique and reveals substantial biases in genetic diversity analyses of high incomplete genotype data with genotype imputations. These findings indicate that genetic diversity analysis of highly incomplete GBS genotype data could be reliably performed, but requires caution with respect to analysis goal, missing level and imputation application. The findings reported here are also instructive for performing a proper genetic diversity analysis of highly incomplete GBS or other genotype data.

901–911 **Effects of Sample Selection Bias on the Accuracy of Population Structure and Ancestry Inference**
Suyash Shringarpure and Eric P. Xing

Model-based likelihood methods and eigenanalysis are commonly used for ancestry inference in samples from populations. However, the sampling procedure can be biased due to logistical constraints or sampling criteria. We study the effects of biased sampling on ancestry inference using model-based methods and eigenanalysis using simulations and real genotype data and demonstrate that it can affect results of ancestry inference. We also show how sampling bias can be modeled mathematically and corrected using simulations.

913–923 **Genetic Linkage Mapping and Transmission Ratio Distortion in a Three-Generation Four-Founder Population of *Panicum virgatum* (L.)**
Guifen Li, Desalegn D. Serba, Malay C. Saha, Joseph H. Bouton, Christina L. Lanzatella, and Christian M. Tobias

This linkage mapping study was conducted in order to allow identification of genetic regions controlling biomass traits such as yield and cell wall composition in switchgrass. Having a three-generation pedigree simplifies identification of these regions by giving prior knowledge of which markers and traits are physically located on the same chromosome segment.

925–929 **Efficient Gene Knock-out and Knock-in with Transgenic Cas9 in *Drosophila***
Zhaoyu Xue, Mengda Ren, Menghua Wu, Junbiao Dai, Yikang S. Rong, and Guanjun Gao

Gene targeting plays an important role in explaining gene function. Recently, the RNA-guided CRISPR/Cas9 system has been successfully used for the purpose of genome editing in many organisms, including *Drosophila*. However, the usual method relying on Cas9-mRNA injection could be challenging to inexperienced researchers, which could result in inconsistencies in mutational efficiency. We improve this method by developing a transgenic system that expresses Cas9 in the *Drosophila* germline, which shows efficient gene targeting, including knock-in. This is an important reagent for *Drosophila* researchers.

931–940 **Phenotypic Analysis of a Family of Transcriptional Regulators, the Zinc Cluster Proteins, in the Human Fungal Pathogen *Candida glabrata***
Natalia Klimova, Ralph Yeung, Nadezda Kachurina, and Bernard Turcotte

Candida glabrata is the second most important human fungal pathogen but less is known about the biology of this organism, as compared to budding yeast. This is particularly true when looking at zinc cluster proteins that form a very important fungal family of transcriptional regulators. Indeed, only few zinc cluster proteins have been characterized in *C. glabrata*. In this study, we have generated a panel of deletion strains of non-essential zinc cluster genes. Using our panel of deletion strains, we have performed phenotypic analysis under various conditions. For example, we show that some zinc cluster proteins mediate drug resistance.

941 **CORRIGENDUM**