ISSUE HIGHLIGHTS

The mother enrichment program: A genetic system for facile replicative life span analysis in *Saccharomyces cerevisiae*, pp. 413–422

Derek L. Lindstrom and Daniel E. Gottschling

Saccharomyces cerevisiae provides a unique opportunity to study replicative aging, but the field has been hampered for 50 years by the requirement to physically separate mother and daughter cells to measure replicative life span. To overcome this limitation, these authors develop a genetic method to eliminate daughter cells. Under the mother enrichment program, the viability of a population in liquid culture becomes a function of life span, providing a facile new method for measuring and manipulating life span. Removing this impediment to aging studies opens the field to the full potential of yeast molecular and genetic techniques.

Effects of recombination on complex regulatory circuits, pp. 673–684

Olivier C. Martin and Andreas Wagner

Mutation and recombination are the two main forces generating genetic variation. Because recombination can reorganize genetic interactions, it may have much greater consequences than point mutations. These investigators explore the effects of recombination on models of transcriptional regulatory circuits that play important roles in embryonic development. They show that recombination has weaker deleterious effects on the expression phenotypes of these circuits than do mutations. In addition, if a population of such circuits evolves under the influence of mutation and recombination, they show that robustness and genetic diversity are strongly enhanced through the appearance of *cis*-regulatory complexes.

In *Saccharomyces cerevisiae*, yKu and subtelomeric core X sequences repress homologous recombination near telomeres as part of the same pathway, pp. 441–451

Marcus E. Marvin, Craig D. Griffin, David E. Eyre, David B. H. Barton and Edward J. Louis

The ends of chromosomes and the adjacent subtelomeric sequences appear to undergo frequent recombination with each other. Such recurrent rearrangements would be detrimental if they occurred throughout the genome, so an important question to answer is this: How is this recombination kept under control and prevented from destroying the genome? This article shows that the yKu complex, in conjunction with a particular subtelomeric sequence called core X, represses recombination near telomeres. This study reveals a potential function of subtelomeric sequences and adds to the numerous telomere functions of the yKu complex.

Alcohol sensitivity in Drosophila: Translational potential of systems genetics, pp. 733–745

Tatiana V. Morozova, Julien F. Ayroles, Katherine W. Jordan, Laura H. Duncan, Mary Anna Carbone, Richard F. Lyman, Eric A. Stone, Diddahally R. Govindaraju, R. Curtis Ellison, Trudy F. C. Mackay and Robert R. H. Anholt

Using genomewide association studies to identify risk alleles for human behavioral disorders has been hampered by a daunting multiple testing problem and an inability to control genetic background and environmental variation. These investigators ameliorate these problems by combining a genomewide study in a model organism with candidate gene association analyses in human populations. They characterize genetic networks that underlie the response to ethanol exposure in *Drosophila melanogaster* and use this information to identify candidate genes associated with alcohol-drinking behavior in a human population. They find that variation in a gene for malic enzyme contributes to variation in cocktail drinking.

Effects of chromosomal rearrangements on transvection at the *yellow* gene of *Drosophila melanogaster*, pp. 483–496

Sharon A. Ou, Elaine Chang, Szexian Lee, Katherine So, C.-ting Wu and James R. Morris

How can a large amount of DNA be packaged into a small nucleus but still be faithfully expressed, replicated, and passed through cell divisions? The authors of this article address that question by studying a conspicuous aspect of nuclear organization in Drosophila—chromosome pairing. In Drosophila, homologous chromosomes are paired in somatic cells and expression of some genes is sensitive to pairing, a phenomenon known as transvection. The authors examine pairing requirements for expression of the *yellow* gene, and they define a small region close to *yellow* that needs to be intact for transvection to occur.

Phenotypic consequences of purine nucleotide imbalance in *Saccharomyces cerevisiae*, pp. 529–538

Christelle Saint-Marc, Benoît Pinson, Fanny Coulpier, Laurent Jourdren, Olesia Lisova and Bertrand Daignan-Fornier

This study underscores the sensitivity of cells to nucleotide imbalance. The authors show that AMP deaminase (AMPD) is critical for growth and proper purine nucleotide balance in yeast. This article provides insight into the physiological role of AMPD and establishes the transcriptional profile of guanylic nucleotide depleted cells. Since AMPD deficiency is the most common muscle enzyme defect in humans, and because inhibitors of guanylic nucleotide synthesis are potent immunosuppressive drugs, this work has immediate implications for human health.

Comparing mutational and standing genetic variability for fitness and size in *Caenorhabditis briggsae* and *C. elegans*, pp. 685–692

Matthew P. Salomon, Dejerianne Ostrow, Naomi Phillips, Dustin Blanton, Whitney Bour, Thomas E. Keller, Laura Levy, Thamar Sylvestre, Ambuj Upadhyay and Charles F. Baer

The genetic variation present in a species is a complicated function of mutation, selection, and population size. Differences in the level of standing genetic variation among groups of organisms have largely focused on selection and population size. Studying two species of self-fertile roundworms that are thought to differ in their mutation rate, these authors obtain results that are consistent with the idea that differences in mutation rate can explain differences in genetic variation. However, random hitchhiking ("genetic draft") is an intriguing possible alternative explanation.

***Cis*-regulatory changes at *FLOWERING LOCUS T* mediate natural variation in flowering responses of *Arabidopsis thaliana*, pp. 723–732**

Christopher Schwartz, Sureshkumar Balasubramanian, Norman Warthmann, Todd P. Michael, Janne Lempe, Sridevi Sureshkumar, Yasushi Kobayashi, Julin N. Maloof, Justin O. Borevitz, Joanne Chory and Detlef Weigel

Finding quantitative trait loci remains a laborious task. These authors introduce a new approach that they dub "quantitative knockdown" to demonstrate that *cis*-regulatory variation in one of the central regulators of flowering contributes to natural variation in this important adaptive trait in *Arabidopsis thaliana*.

This Month in Genetics Research

Rare, evolutionarily unlikely missense substitutions in *ATM* confer increased risk of breast cancer, Am. J. Hum. Genet. 85: 427–446

Sean V. Tavtigian, Peter J. Oefner, Davit Babikyan, Anne Hartmann, Sue Healey, Florence Le Calvez-Kelm, Fabienne Lesueur, Graham B. Byrnes, Shu-Chun Chuang, Nathalie Forey, Corinna Feuchtinger, Lydie Gioia, Janet Hall, Mia Hashibe, Barbara Herte, Sandrine McKay-Chopin, Alun Thomas, Maxime P. Vallée, Catherine Voegele, Penelope M. Webb, David C. Whiteman, Australian Cancer Study, Breast Cancer Family Registries (BCFR), Kathleen Cuningham Foundation Consortium for Research into Familial Aspects of Breast Cancer (kConFab), Suleeporn Sangrajrang, John L. Hopper, Melissa C. Southey, Irene L. Andrulis, Esther M. John and Georgia Chenevix-Trench

Identifying mutations in genes that confer intermediate or low susceptibility to disease is challenging. This article attacks the problem for *ATM*, an intermediate-risk breast cancer gene. By sequencing *ATM* from several thousand breast cancer cases and controls, the authors obtain evidence that rare, evolutionarily unlikely missense mutations in *ATM* account for a disproportionate amount of risk for the disease. This is not good news, because it means that a daunting number of subjects will need to be screened to identify these risky sequence variants.