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Genetic variation in *Saccharomyces cerevisiae*: Circuit diversification in a signal transduction network, pp. 1523–1532

Brian L. Chin, Owen Ryan, Fran Lewitter, Charles Boone, and Gerald R. Fink

The plummeting cost of genome sequencing has revealed increasing amounts of genetic variation within a species. How much of that variation affects function, and how might it help us understand evolution? The authors addressed these questions by looking at how cell adhesion is controlled in two closely related yeast strains. Despite their similar genomic sequences, these two strains use different sets of genes to regulate adhesion. A signal transduction pathway has been rewired, partly because of polymorphisms in a transcription factor.

Gene functional trade-offs and the evolution of pleiotropy, pp. 1389–1409

Frédéric Guillaume and Sarah P. Otto

Pleiotropy—the property of genes affecting multiple features of an organism—is often considered to be an unavoidable by-product of a gene's evolutionary history. These authors explored how the pleiotropic degree of a gene may evolve, providing clues to why pleiotropy varies among genes. They found two common outcomes of the evolution of multifunctional genes: increased pleiotropy of genes more highly expressed, and specialization of all genes on the trait most important to fitness.

Receptors and other signaling proteins required for serotonin control of locomotion in *Caenorhabditis elegans*, pp. 1359–1371

Güliz Gürel, Megan A. Gustafson, Judy S. Pepper, H. Robert Horvitz, and Michael R. Koelle

This article offers insight into the mechanism of signaling by serotonin, a neurotransmitter involved in mood disorders in humans. The authors carried out screens for *C. elegans* mutants that fail to respond properly to this neurotransmitter, which worms use to control locomotion. They identified mutations in more than eight genes required for serotonin signaling. Two encode serotonin receptors, while the others encode proteins that in some cases are implicated for the first time in serotonin signaling by this work. There are similar human proteins that may mediate serotonin signaling in our brains. The two *C. elegans* serotonin receptors appear to act in parallel in different cells to coordinate behavioral responses to serotonin.

Long-term and short-term evolutionary impacts of transposable elements on *Drosophila*, pp. 1411–1432

Yuh Chwen G. Lee and Charles H. Langley

Transposable elements are ubiquitous genomic parasites. Even though they are primarily vertically inherited as part of the genome, their interactions with the host are often likened to the coevolution of host genes and non-genomic, horizontally transferred pathogens. Here Lee and Langley show that genes involved in the interaction with transposable elements indeed show strong signals of positive selection similar to those of immunity genes in *Drosophila*, but with a fundamentally different mechanism from that of host-pathogen coevolution.

Unusual and typical features of a novel *restorer-of-fertility* gene of sugar beet (*Beta vulgaris* L.), pp. 1347–1358

Hiroaki Matsuhira, Hiroyo Kagami, Masayuki Kurata, Kazuyoshi Kitazaki, Muneyuki Matsunaga, Yuko Hamaguchi, Eiki Hagihara, Minoru Ueda, Michiyo Harada, Aki Muramatsu, Rika Yui-Kurino, Kazunori Taguchi, Hideto Tamagake, Tetsuo Mikami, and Tomohiko Kubo

Plant pollen production is often impaired by incompatibility between the mitochondria and nucleus. A nuclear gene termed *Rf* can cancel this cytoplasmic male sterility. These authors report that sugar beet *Rf* encodes a metalloprotease-like gene, in contrast to other *Rf*s which encode proteins supposed to bind RNA. Interestingly, the sugar beet *Rf* locus exhibits the gene clustering often seen in plant *Rf* loci, suggesting a common evolutionary mechanism regardless of the *Rf* gene products.

CloudMap: A cloud-based pipeline for analysis of mutant genome sequences, pp. 1249–1269

Gregory Minevich, Danny S. Park, Daniel Blankenberg, Richard J. Poole, and Oliver Hobert

This article describes a cloud-based data-analysis pipeline that greatly simplifies analysis of mutant genome sequences. Available on the Galaxy platform, CloudMap requires no software installation and is modular, and thus able to accommodate new software tools as they become available. CloudMap uses a series of predefined workflows, allowing users to arrive at a mapping region and a list of variants with a few clicks.

Epigenetic regulation of axonal growth of *Drosophila* pacemaker cells by histone acetyltransferase Tip60 controls sleep, pp. 1327–1345

Sheila K. Pirooznia, Kellie Chiu, May T. Chan, John E. Zimmerman, and Felice Elefant

This article provides insight into sleep disturbances caused by neurodegenerative diseases. In *Drosophila*, misregulation of the histone acetyltransferase Tip60 causes sleep disturbances similar to those seen in Alzheimer's disease patients, with nighttime sleep disruption and daytime sleepiness. These authors show that Tip60 interacts with amyloid precursor protein (APP) to mediate axonal growth of *Drosophila* pacemaker cells and their production of a neuropeptide that stabilizes sleep–wake cycles. Remarkably, excess Tip60 rescues sleep disruption caused by APP-induced neurodegenerative conditions.

Genetic basis of a violation of Dollo's law: Re-evolution of rotating sex combs in *Drosophila bipectinata*, pp. 1465–1475

Thaddeus Seher, Chen Siang Ng, Sarah Signor, Ondrej Podlaha, Olga Barmina, and Artyom Kopp

"Dollo's law" posits that complex traits, once lost during evolution, cannot be regained. However, phylogenetic analyses reveal occasional violations of this law. This article describes the genetic basis of one such reversal. Rotated sex combs were lost and subsequently regained in the *ananassae* species subgroup of *Drosophila*. This reversal is largely associated with one chromosomal inversion that covers 5% of the genome, suggesting that rotating sex combs may have re-evolved though changes in relatively few genes.

A comprehensive genetic approach for improving prediction of skin cancer risk in humans, pp. 1493–1502

Ana I. Vazquez, Gustavo de los Campos, Yann C. Klimentidis, Guilherme J. M. Rosa, Daniel Gianola, Nengjun Yi, and David B. Allison

Predicting complex traits in humans is difficult because most of the genetic variance remains unaccounted for and many small-effect genes are usually involved. These investigators developed several models for predicting skin cancer risk. Prediction improved significantly when genetic parameters such as family history and geographical ancestry were included, especially when thousands of markers across the genome were considered. These methods could be extended to prediction of other diseases.

This Month's Perspectives

Mammalian developmental genetics in the twentieth century, pp. 1151–1163

Karen Artzt

This Perspectives reviews the breathtaking history of mammalian genetics in the past century from a mouse developmental geneticist's point of view. The dizzying speed of progress is illustrated with selected examples of genetic enigmas now solved and includes a retrospective discussion of the *T/t* complex. It is a story of how hypothesis-driven research got us where we are. These stories should be of interest especially to younger geneticists.

This Month in the American Journal of Human Genetics

Deleterious and disease alleles prevalence in healthy individuals: Insights from current predictions, mutations databases and population-scale resequencing. Am. J. Hum. Genet. 91(6)

Yali Xue, Yuan Chen, Qasim Ayub, Ni Huang, Edward V. Ball, Matthew Mort, Andrew D. Phillips, Katy Shaw, Peter D. Stenson, David N. Cooper, Chris Tyler-Smith

Personalized medicine is dependent on accurate annotation of disease causing mutations, and missense variants require especially careful interpretation. This analysis of sequences from the 1000 Genomes Pilot Project reveals that healthy individuals harbor 40-85 damaging homozygous missense mutations, of which 3-24 are annotated as disease-causing in the Human Gene Mutation Database. Further analysis suggests that some of the variants annotated as disease causing are not pathogenic. Such refinement of annotations is sure to improve genetic testing and treatment.