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Empirical complexities in the genetic foundations of lethal mutagenesis, pp. 541–552

James J. Bull, Paul Joyce, Eric Gladstone, and Ian J. Molineux

Ramping up the mutation rate of viruses has been touted as an option for treatment of infection, but the genetic and evolutionary foundations of this approach are poorly connected to theory. The single empirical test of the theory was a profound failure: viral fitness increased rather than decreased. Here Bull and colleagues explore reasons for the disconnect between theory and observations, suggesting that the fitness consequences of mutations are not nearly as deleterious as expected. Efforts at 'lethal mutagenesis' may thus commonly augment adaptation rather than thwart it.

A novel approach to estimating heterozygosity from low-coverage genome sequence, pp. 553–561

Katarzyna Bryc, Nick Patterson, and David Reich

Heterozygosity may be the single most informative statistic in characterizing the level of genetic variation in a genome. The authors of this article developed a novel approach to estimate heterozygosity with as little as 4X sequence coverage of a genome. Their in-depth analysis reveals that estimates of heterozygosity are significantly elevated at regions of perceived higher sequence coverage, which has significant implications for analysis of sequence data.

Predicting functionally informative mutations in *Escherichia coli* BamA using evolutionary covariance analysis, pp. 443–455

Robert S. Dwyer, Dante P. Ricci, Lucy J. Colwell, Thomas J. Silhavy, and Ned S. Wingreen

Covariance analysis identifies coordinated amino acid substitutions among orthologs and can predict functional interactions among amino acids. Dwyer *et al.* show that the Direct Coupling Analysis (DCA) covariance approach works well for large β-barrel proteins and apply it to the *Escherichia coli* OMP assembly machine component BamA. They identify a residue pair that stabilizes the BamA beta-barrel and provide evidence that the residues are functionally related. DCA could aid the study of genes for which direct selections are lacking.

Integration profiling of gene function with dense maps of transposon integration, pp. 599–609

Yabin Guo, Jung Min Park, Bowen Cui, Elizabeth Humes, Sunil Gangadharan, Stevephen Hung, Peter C. FitzGerald, Kwang-Lae Hoe, Shiv I. S. Grewal, Nancy L. Craig, and Henry L. Levin

This article describes a transposon-based method called integration profiling that uses high-density maps of insertions to identify genes required for cell division. The method was used to identify accurately essential genes of *Schizosaccharomyces pombe* and measure how much they contribute to growth. Integration profiling has the potential to identify genes important for many other functions such as DNA repair, stress response, and meiosis.

Accumulation of spontaneous mutations in the ciliate *Tetrahymena thermophila*, pp. 527–540

Hong-An Long, Tiago Paixão, Ricardo B. R. Azevedo, and Rebecca A. Zufall

The rate at which mutations occur, and their consequences for the fitness of an organism, are among the most important parameters in evolutionary theory, but they are difficult to measure. This article introduces a new way to study these parameters using the ciliate *Tetrahymena thermophila*, which accumulates mutations in a nucleus that is never exposed to natural selection, allowing the authors an unfiltered look at how mutations affect this single-celled organism.

Precise and heritable genome editing in evolutionarily diverse nematodes using TALENs and CRISPR/Cas9 to engineer insertions and deletions, pp. 331–348

Te-Wen Lo, Catherine S. Pickle, Steven Lin, Edward J. Ralston, Mark Gurling, Caitlin M. Schartner, Qian Bian, Jennifer A. Doudna, and Barbara J. Meyer

This is the second of several articles in the journal describing exciting new methods for precise engineering of genomes. This article describes strategies to create precise, heritable mutations of any selected locus in *Nematode* species spanning 300 MYR of evolutionary divergence, from *Caenorhabditis* species to *Pristionchus* species, using TALE and CRISPR/Cas9 nucleases, bringing genetic tractability to non-model nematode species. A Commentary by Kent Golic discusses similar advances in *Drosophila* (see article in last month's issue by Yu *et al.* 10.1534/genetics.113.153825). Five more articles describing genome editing of *Caenorhabditis elegans* using the CRISPR/Cas9 nuclease will appear next month. Suddenly, yeast's is not the only genome that can be engineered at will.

Association of maternal mRNA and phosphorylated EIF4EBP1 variants with the spindle in mouse oocytes: localized translational control supporting female meiosis in mammals, pp. 349–358

Edward J. Romasko, Dasari Amarnath, Uros Midic, and Keith E. Latham

In contrast to other species, localized maternal mRNAs are not believed to be prevalent in mammalian oocytes. But this article reports that maternal mRNAs encoding spindle/cytoskeleton, chromatin/nuclear, signaling and other proteins are enriched at the spindle-chromosome complex in mouse metaphase II stage oocytes. Because the translation regulator EIF4EBP1 becomes localized to the spindle and kinetochores at each meiotic metaphase, the authors surmise that localized translational control may contribute to the formation and function of spindles, coordinating events during meiosis to ensure proper segregation of genetic material.

Rare variants in hypermutable genes underlie common morphology and growth traits in wild *Saccharomyces paradoxus*, pp. 513–525

Jeremy I. Roop and Rachel B. Brem

What are the relative contributions of rare and common variants to common trait differences? Roop and Brem discovered that rare, unrelated alleles of homologs of the hypermutable human neurofibromatosis gene, NF1, influence hundreds of common traits in wild yeasts. Their results implicate rare variants in yeast morphology, stress resistance, and metabolism, and suggest that the hypermutability of a prominent human disease locus originated millions of years ago in a unicellular ancestor.

Clustering and protein dynamics of *Drosophila melanogaster* telomeres, pp. 381–391

Natalia Wesolowska, Flavia L. Amariei, and Yikang S. Rong

Telomere organization may contribute to the architecture of the nucleus. This article demonstrates that clustering of telomeres is a characteristic of nuclear organization conserved through evolution, and that the fruit fly is a good model for its study. The reported results argue against recombination or DNA homology as the main mediators of telomeric clustering, and point to an unidentified component common to all telomeres that mediates their clustering.

This Month's Perspectives

Georges Teissier (1900-1972) and the modern synthesis in France, pp. 295–302

Laurent Loison

This month's Perspectives is devoted to the tortuous history of the evolutionary synthesis in France between 1930-1960. Laurent Loison focuses on the ideas of the zoologist Georges Teissier, one of the very few Darwinians in France at that time. The author argues that Teissier was a true zoologist, not a mathematician who had only secondarily become interested in zoology. As a zoologist, Teissier was completely aware of the neo-Lamarckian context in France. This paper also describes the ways Teissier, during the 1950s, conceptualized the mechanisms that could allow for macroevolutionary transitions.

This Month in the American Journal of Human Genetics

Genetic mapping with multiple levels of phenotypic information reveals determinants of lymphocyte glucocorticoid sensitivity, Am. J. Hum. Gent. 93(4)

Joseph C. Maranville, Shaneen S. Baxter, David B. Witonsky, Meredith A. Chase, and Anna Di Rienzo

Glucocorticoid steroids effect transcriptional changes through the glucocorticoid receptor. Individuals differ dramatically in their sensitivity to glucocorticoid, likely due to differences in transcription. Maranville *et al.* identified a glucocorticoid-responsive QTL associated with transcriptional changes at many genes that appears to be a *cis*-regulatory polymorphism for *RBMS3*, known to be involved in the glucocorticoid response, and a *trans*-regulatory polymorphism for many other genes involved in the steroid response.