

Determinants of genetic diversity of spontaneous drug resistance in bacteria, pp. 1369–1380*Alejandro Couce, Alexandro Rodríguez-Rojas, and Jesús Blázquez*

A microbial population's capacity to cope with second-line antibiotics can depend on its genetic diversity at resistance loci. How this diversity accumulates before antibiotic treatment is poorly understood. Combining theory and experiments, Couce *et al.* find that diversity is extremely sensitive to variations in the fitness effects of resistance. Indeed, a slight fitness advantage of the mutant over the wild-type is enough to keep diversity low and independent of population size. These insights will assist the fight against multi-drug resistant microbes, as well as efforts to predict cancer evolution.

Buffering of genetic regulatory networks in *Drosophila melanogaster*, pp. 1177–1190*Justin M. Fear, Luis G. León-Novelo, Alison M. Morse, Alison R. Gerken, Kjong Van Lehmann, John Tower, Sergey V. Nuzhdin, and Lauren M. McIntyre*

A strong consensus is emerging from gene regulation analyses in model organisms: *cis* and *trans* effects are compensatory. This phylogenetically ubiquitous pattern is frequently postulated to be the result of co-evolution. But within species, *cis* and *trans* effects cannot co-evolve as they are not co-transmitted. Fear *et al.* propose that the compensatory nature of *cis* and *trans* effects explains widespread observations of gene regulatory network (GRN) robustness. This provides a bridge between molecular models of GRN and genome-wide models of regulatory variation where both point to large scale robustness.

Epistasis and the dynamics of reversion in molecular evolution, pp. 1335–1351*David M. McCandlish, Premal Shah, and Joshua B. Plotkin*

Evolutionary geneticists have speculated that the longer a mutation has been fixed in a population, the more difficult it is to revert – *i.e.* to be replaced by its ancestral allele. Indeed, recent empirical and simulation studies suggest that this phenomenon of entrenchment is ubiquitous in protein evolution. McCandlish *et al.* provide a rigorous mathematical exploration of reversions, demonstrating that reversion rates will always decrease with time when the effects of mutations depend upon the genetic background.

Long-term memory in *Drosophila* is influenced by histone deacetylase HDAC4 interacting with SUMO-conjugating enzyme Ubc9, pp. 1249–1264*Silvia Schwartz, Mauro Truglio, Maxwell J. Scott, and Helen L. Fitzsimons*

Haploinsufficiency of the histone deacetylase HDAC4 results in intellectual disability in humans and reduction of HDAC4 impairs memory in animal models. However, increasing evidence suggests HDAC4 has essential non-nuclear roles beyond transcriptional regulation. Schwartz *et al.* performed an enhancer screen in *Drosophila* and identified 26 genes that interacted genetically with HDAC4. These included genes that regulate axon and/or dendritic growth through rearrangement of the actin cytoskeleton, and genes that regulate SUMOylation, an important process in memory formation. Moreover, they showed that the SUMO-conjugating enzyme Ubc9 interacts with HDAC4 during memory formation.

Heterozygote advantage is a common outcome of adaptation in *Saccharomyces cerevisiae*, pp. 1401–1413*Diamantis Sellis, Daniel J. Kvittek, Barbara Dunn, Gavin Sherlock, and Dmitri A. Petrov*

Adaptation in diploids has been predicted theoretically to follow different dynamics than adaptation in haploids. Adaptive mutations in diploids are expected to exhibit heterozygous advantage allowing directional selection to generate and maintain abundant

genetic variation rather than to remove it. However, despite the broad implications for our understanding of adaptation, empirical evidence for heterozygote advantage in adapting populations has been lacking. Sellis *et al.* experimentally test this prediction and find strong evidence in its favor.

Genomic conflicts that cause pollen mortality and raise reproductive barriers in *Arabidopsis thaliana*, pp. 1353–1367*Matthieu Simon, Stéphanie Durand, Natacha Pluta, Nicolas Gobron, Lucy Botran, Anthony Ricou, Christine Camilleri, and Françoise Budar*

In plants, an important component of postzygotic reproductive isolation is hybrid sterility. Simon *et al.* dissect the complex genetic architecture of *Arabidopsis thaliana* intraspecific hybrid male sterility. They find that hybrid sterility results from the combination and genetic linkage of pollen killer (PK) loci and gametophytic cytoplasmic male-sterility (CMS) loci. These results suggest that genomic conflicts underlying the evolution of PK and CMS create reproductive barriers between distant strains within a species, which may eventually lead to speciation.

Increased proportion of variance explained and prediction accuracy of survival of breast cancer patients with use of whole-genome multiomic profiles, pp. 1425–1438*Ana I. Vazquez, Yogasudha Veturi, Michael Behring, Sadeep Shrestha, Matias Kirst, Marcio F. R. Resende, Jr., and Gustavo de los Campos*

Multi-omic information can be used to illuminate disease processes and develop risk assessments. Vazquez *et al.* describe a statistical framework for predicting disease risk by integrating multi-layer high-dimensional omics with clinical covariates. They use data from The Cancer Genome Atlas to develop models for breast cancer survival. Whole-genome gene expression profiles were more predictive of survival than any of the commonly used clinical covariates, including cancer subtype and stage.

Synaptonemal complex proteins of budding yeast define reciprocal roles in mut γ -mediated crossover formation, pp. 1091–1103*Karen Voelkel-Meiman, Shun-Yun Cheng, Savannah J. Morehouse, and Amy J. MacQueen*

The meiosis-specific, proteinaceous synaptonemal complex (SC) structure is a widely conserved feature of meiotic chromosomes undergoing recombination, and the vast majority of genetic data indicate a role for the SC in promoting crossovers. Voelkel-Meiman *et al.* describe an unanticipated result, finding that budding yeast mutants missing a specific subset of SC structural proteins display more crossover events, instead of the decrease that is characteristic of previously described SC-deficient mutants.

This Month in the American Journal of Human Genetics**Contrasting the genetic architecture of 30 complex traits from summary association data, *Am. J. Hum. Genet.* 99(1)***Huwenbo Shi, Gleb Kichaev, and Bogdan Pasaniuc*

Although genome-wide association studies have made it possible to identify SNPs associated with numerous traits, index SNPs are able to explain only a fraction of the variance in a given trait. Methods devised to estimate overall SNP-heritability often suffer from invalid underlying assumptions related to causality. To address this problem, Shi *et al.* developed Heritability Estimator from Summary Statistics (HESS), a method that estimates the variance in a given trait explained by all typed SNPs at a single locus while also accounting for linkage disequilibrium (LD) among SNPs. Among their key findings, the authors identify thirty-six 'heritability hotspots,' discrete regions of the genome that make significant contributions to the SNP-heritability of multiple traits.