Massively parallel sequencing (MPS) has revolutionized genomics but sequencing large amounts of DNA across many individuals is often cost-prohibitive or unnecessary. This study presents a rapid and flexible method for analyzing MPS data across individuals and genomic loci called Rapture (RAD Capture). This method combines the benefits of RAD sequencing and sequence capture. Rapture can process many individuals with minimal library preparation and sequencing costs, which makes genetic analysis more efficient for many applications.

Exploiting linkage disequilibrium for ultrahigh-dimensional genome-wide data with an integrated statistical approach, pp. 411–426
Michelle Carlsen, Guijiang Fu, Shaun Bushman, and Christopher Corcoran

Carlsen et al. present improved methods for analysis of genome-wide association studies. Currently, up to a million single-nucleotide polymorphisms (SNPs) can be feasibly generated within any given population, but there are often correlations among SNPs that cause truly causative loci to be confounded by correlated neighbors. Additionally, complex traits are often jointly affected by multiple genetic variants with small or moderate individual effects. The authors propose a novel statistical approach, DCRR, to detecting significant associations between large numbers of SNPs and phenotypes.

Differential masking of natural genetic variation by miR-9a in Drosophila, pp. 675–687
Justin J. Cassidy, Alexander J. Straughan, and Richard W. Carthew

Genetic variation is rarely deterministic for phenotypic traits, but instead has mainly probabilistic effects on outcome. The reasons are largely unknown but it has been suspected that active mechanisms may buffer the impact of genetic variation. Using artificial selection in Drosophila, Cassidy et al. find that the non-coding microRNA miR-9a is part of such a mechanism. Their results suggest that miR-9a modulates genetic variation into a landscape in which variants’ impact is masked by miR-9a for some but not all traits.

A delicate balance between repair and replication factors regulates recombination between divergent DNA sequences in Saccharomyces cerevisiae, pp. 525–540
Ujani Chakraborty, Carolyn M. George, Amy M. Lyndaker, and Eric Alani

Homologous recombination between divergent, non-allelic DNA sequences can lead to deleterious genome rearrangements. To suppress single-strand annealing between divergent sequences, the Msh DNA mismatch recognition complex and Sgs1 helicase bind to mismatches in heteroduplex DNA intermediates and trigger an unwinding mechanism known as heteroduplex rejection. Chakraborty et al. show that Top3-Rmi1, a topoisomerase complex that interacts with Sgs1, is required for heteroduplex rejection. Msh6 overexpression significantly increases heteroduplex rejection due to a compromise in Msh2-Msh3 function required for 3′ tail clamping during single-strand annealing. This indicates that tail clamping is a critical regulatory step in the rejection vs. repair decision.

Genetic architectures of quantitative variation in RNA editing pathways, pp. 789–798

RNA editing involves post-transcriptional modification of mRNA nucleotide sequences. Gu et al. investigated the degree to which RNA editing is influenced by genetic variation in a genetically diverse mouse population. They found that variation in ApoB-1 influences global levels of C-to-U editing and that most A-to-I editing is influenced by local genetic variants that may alter the secondary structure of the RNA and hence alter the editing efficiency.

The role of recombination in evolutionary rescue, pp. 721–732
Hildegard Uecker and Joachim Hermisson

How likely is it that a population escapes extinction through adaptive evolution? The answer is of great relevance in conservation biology, and in the management of pesticide or drug resistance. By reshuffling the genome, recombination has two antagonistic effects on the probability of evolutionary rescue: while it generates favorable gene combinations, it also breaks them up. Analysis of a mathematical model reveals a complex dependence of rescue on recombination. Counterintuitively, rapid eradication of the wildtype can promote rescue in the presence of recombination.

An equation to predict the accuracy of genomic values by combining data from multiple traits, populations, or environments, pp. 799–823
Yvonne C. J. Wientjes, Pieter Bijma, Roel F. Veerkamp, and Mario P. L. Calus

Combining individuals from different populations is currently an important area of research for increasing the accuracy of genomic prediction, both for selecting the best animals and plants as well as for predicting the genetic risk of human diseases. In this paper, a deterministic equation is derived to predict the accuracy of genomic values when different populations are combined in the training population, for example from different breeds, lines, environments or genetic backgrounds, or populations measured for different traits. The equation can accurately predict the genomic prediction accuracy for these different scenarios.

Nucleosomes are essential for proper regulation of a multigated promoter in Saccharomyces cerevisiae, pp. 551–563
Robert M. Warrington, Jenna M. Goodrum, and David J. Stillman

How does chromatin repress transcription in a complex promoter? The authors have shown that the yeast HO promoter contains multiple gates that must be opened in sequence for activation. The promoter carries SBF binding sites embedded within nucleosomes so that SBF binding requires help from an upstream promoter element. Here, Warrington et al. modify the HO promoter so that the SBF sites are in a nucleosome free region, and showed that nucleosomes are required for a multigated promoter and its complex regulatory properties.

This Month in the American Journal of Human Genetics

Mitotic intragenic recombination: a mechanism of survival for several congenital disorders of glycosylation, Am. J. Hum. Gen. 98(2)
Megan S. Kane, Mariska Davids, Christopher Adams, Lynne A. Wolfe, Helen W. Cheung, Andrea Gropman, Yu Huang, NISC Comparative Sequencing Program, Bobby G. Ng, Hudson H. Freeze, David R. Adams, William A. Gahl, and Cornelius F. Boerkoel

Congenital disorders of glycosylation (CDG) are caused by defects in enzymes that are important for protein glycosylation. It is rare for an affected individual to have homozygous mutations and the penetrance and phenotypic expressivity vary widely across individuals with mutations in the same gene. In this study, Kane et al. used various sequencing approaches to identify non-parental genotypes in siblings with MOGS mutations who had much longer survival times compared to other affected individuals. This observation could be extended to individuals with mutations in additional CDG-associated genes, suggesting that mitotic recombination might provide a selective advantage to cells through improved enzyme function leading to reduced phenotypic severity in certain individuals.