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The nature of genetic variation for complex traits revealed by GWAS and regional heritability mapping analyses, pp. 1601–1613

Armando Caballero, Albert Tenesa, and Peter D. Keightley

Caballero *et al.* used simulations to show that, contrary to previous results, common variants of large effect are responsible for most of the genetic variation for quantitative traits (except when the trait is fitness itself). They also show that knowledge of full sequence data and multi-SNP methods are unlikely to substantially reduce missing heritability, because additional QTLs revealed by more powerful methods only modestly increase the proportion of the heritability explained.

Paramutation in *Drosophila* requires both nuclear and cytoplasmic actors of the piRNA pathway and induces *cis*-spreading of piRNA production, pp. 1381–1396

Catherine Hermant, Antoine Boivin, Laure Teysset, Valérie Delmarre, Amna Asif-Laidin, Marius van den Beek, Christophe Antoniewski, and Stéphane Ronsseray

Mobile DNA is repressed in animal gonads by non-coding small RNAs called Piwi-Interacting RNAs (piRNAs). In Drosophila the capacity of a genomic locus to produce piRNAs can be transferred from a producing locus to the allelic previously non-producing homologous locus, resulting in an epigenetic conversion process termed paramutation. These authors show that this paramutation event involves nuclear and cytoplasmic components of the piRNA machinery. In addition, since paramutagenic conversion is also shown to occur between partially homologous non-allelic loci, it likely plays an important role in shaping of the epigenome in the wild.

A gene regulatory program in human breast cancer, pp. 1341–1348

Renhua Li, John Campos, and Joji Iida

Li *et al.* identified master regulator genes that shape different tumor subtypes in human breast cancer. Using a machine learning algorigthm, they identified 16 such genes. On the basis of gene expression patterns across three large cohorts of human breast cancer populations, the genes can be congruently divided into two groups that regulate cancer related genes in opposite directions. Their studies define a gene regulatory program for tumor progression.

Selective strolls: fixation and extinction in diploids are slower for weakly selected mutations than for neutral ones, pp. 1581–1589

Fabrizio Mafessoni and Michael Lachmann

A common assumption among geneticists is that neutral alleles survive longer in a population than selected variants: negative selection rapidly leads to extinction of deleterious mutations, while advantageous alleles spread faster till fixation. This paper shows that these assumptions are often incorrect. Weakly selected mutations behave in a fashion opposite to strongly selected ones, with slower average fixation and extinction times than neutral alleles. Hence, fixation events due to weak selection will show opposite patterns of statistics used to detect signatures of positive selection.

Roles of nucleoid-associated proteins in stress-induced mutagenic break repair in starving *Escherichia coli,* pp. 1349–1362

Jessica M. Moore, David Magnan, Ana K. Mojica, María Angélica Bravo Núñez, David Bates, Susan M. Rosenberg, and P. J. Hastings

Like eukaryotic chromosomes, bacterial nucleoids have DNA compaction proteins. These nucleoid-associated proteinsare global transcriptional regulators. These investigators show that nucleoid-associated proteins modulate mutagenesis. Mutagenic break repair in *Escherichia coli* is regulated by proteins that detect stress and activate proteins that act on DNA to make mutations, potentially accelerating evolution during stress. Moore *et al.* found that nine of fifteen nucleoid-associated proteins are required for mutagenic break repair; one inhibits it. Six of them regulate stress-responses, which couple mutagenesis to stress and create genetic diversity

Cell differentiation and spatial organization in yeast colonies: role of cell-wall integrity pathway, pp. 1427–1438

Sarah Piccirillo, Rita Morales, Melissa G. White, Keston Smith, Tamas Kapros, and Saul M. Honigberg

This paper reports that yeast colonies partition into two distinct cell layers: an underlying layer of permeable "feeder" cells and an overlying layer of cells undergoing sexual reproduction (meiosis). Activation of a MAPK pathway in the feeder cell layer stimulates cell permeability and indirectly activates meiosis in the upper layer. In stressful or suboptimal environments, more cells in the colony adopt a feeder cell fate, and under these conditions feeder cell development and MAPK pathway activity become more important for sexual development in the overlying layer.

Manipulation of karyotype in *Caenorhabditis elegans* reveals multiple inputs driving pairwise chromosome synapsis during meiosis, pp. 1363–1379

Baptiste Roelens, Mara Schvarzstein, and Anne M. Villeneuve

Roelens *et al.* devised an efficient strategy for generating polyploid derivatives of virtually any *Caenorhabditis elegans* strain, then exploited this ability to manipulate ploidy to experimentally challenge the meiotic program. Their data suggest that three separate inputs contribute to stable pairwise associations (synapsis) between homologous chromosomes during meiosis: 1) recombination-independent assessment of homology near special chromosome sites known as pairing centers, 2) a strong driving force favoring pairwise over multi-partner interactions, and 3) recombination-dependent maturation of homologous synapsis.

Associating multivariate quantitative phenotypes with genetic variants in family samples with a novel kernel machine regression method, pp. 1329–1339

Qi Yan, Daniel E. Weeks, Juan C. Celedón, Hemant K. Tiwari, Bingshan Li, Xiaojing Wang, Wan-Yu Lin, Xiang-Yang Lou, Guimin Gao, Wei Chen, and Nianjun Liu

Recent developments in sequencing technology enables genetic variants to be associated with complex diseases. Jointly testing for association between genetic variants and multiple correlated phenotypes may increase the power to detect causal genes in family-based studies, but familial correlation needs to be appropriately handled. Yan *et al.* propose a novel approach that is based on a linear mixed model framework that can be applied to a large range of studies with different types of traits.

This Month in the American Journal of Human Genetics

Multiple hepatic regulatory variants at the GALNT2 high-density lipoprotein cholesterol GWAS locus, Am. J. Hum. Gent. 98(1)

Tamara S. Roman, Amanda F. Marvelle, Marie P. Fogarty, Swarooparani Vadlamudi, Arlene J. Gonzalez, Martin L. Buchkovich, Jeroen R. Huyghe, Christian Fuchsberger, Anne U. Jackson, Ying Wu, Mete Civelek, Aldons J. Lusis, Kyle J. Gaulton, Praveen Sethupathy, Antti J. Kangas, Pasi Soininen, Mika Ala-Korpela, Johanna Kuusisto, Francis S. Collins, Markku Laakso, Michael Boehnke, and Karen L. Mohlke

GWAS has produced an enormous number of SNPs associated with various traits, but the function of many of these signals is unclear. Experimental follow-up is required to determine the functional variants underlying the signal and the consequences of variation at these sites. In this study, Roman *et al.* fine map a region near *GALNT2*, that is associated with blood lipids and cholesterol levels. At least two variants in LD with the tag-SNP appear to alter transcription factor binding and *GALNT2* expression. Together, these results demonstrate that multiple regulatory variants near *GALNT2*, encoding a gene involved in HDL-C metabolism, might explain the GWAS signal and suggest that future work to determine how GALNT2 influences HDL particle size could be useful in understanding blood lipids in humans.