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Fine mapping causal variants with an approximate Bayesian method using marginal test statistics, pp. 719–736

Wenan Chen, Beth R. Larrabee, Inna G. Ovsyannikova, Richard B. Kennedy, Iana H. Haralambieva, Gregory A. Poland, and Daniel J. Schaid

Most genome-wide association studies (GWAS) reveal only regions of association, while the underlying causal variants remain unclear. Chen *et al.* show that two existing methods for identifying candidate causal variants can be unified in a general Bayesian framework, allowing application of an approximate Bayesian method that uses only the summary information. Through simulations and real data analysis, the authors show the proposed method identified candidate causal variants with high accuracy.

The carboxy-terminal tails of septins Cdc11 and Shs1 recruit myosin-II binding factor Bni5 to the bud neck in *Saccharomyces cerevisiae*, pp. 821–840

Gregory C. Finnigan, Elizabeth A. Booth, Angela Duvalyan, Elizabeth N. Liao, and Jeremy Thorner

AND

Comprehensive genetic analysis of paralogous terminal septin subunits Shs1 and Cdc11 in *Saccharomyces cerevisiae*, pp. 841–861

Gregory C. Finnigan, Julie Takagi, Christina Cho, and Jeremy Thorner

Septins are a family of GTP-binding proteins that self-assemble into higher-order structures. In these companion papers, Finnigan *et al.* analyzed the function of Shs1 and Cdc11, the paralogous terminal subunits of the septin hetero-octamer. Comprehensive analyses revealed the importance of a C-terminal extension that optimizes recruitment of the protein Bni5, thereby ensuring efficient localization of the type II myosin of the actomyosin contractile ring.

Histone sprocket arginine residues are important for gene expression, DNA repair, and cell viability in *Saccharomyces cerevisiae*, pp. 795–806

Amelia J. Hodges, Isaura J. Gallegos, Marian F. Laughery, Rithy Meas, Linh Tran, and John J. Wyrick

Like the teeth of a bicycle sprocket-wheel, the "sprocket" arginine residues of histones insert into the minor groove of the DNA "chain." Hodges *et al.* identify novel functions for histone sprocket arginine residues in gene expression, cryptic transcription, DNA repair, and histone occupancy. These findings reveal simple rules for how the biological function of each "sprocket" residue is influenced by the location and structural mode of DNA binding.

Evaluation of ancestral sequence reconstruction methods to infer nonstationary patterns of nucleotide substitution, pp. 873–890

Tomotaka Matsumoto, Hiroshi Akashi, and Ziheng Yang

To test many hypotheses of molecular sequence evolution, the gene sequences of ancestral species must be inferred. However, the use of reconstructed ancestral sequences may produce spurious results because systematic biases emerge from using the single best reconstructions while ignoring the suboptimal ones, and from model violations. Matsumoto *et al.* developed methods to correct for such biases and used simulation to evaluate their performance when nucleotide substitution patterns are not constant. The authors suggest the new methods may be useful for studying complex patterns of nucleotide substitution in large genomic datasets.

Worldwide population structure, long-term demography, and local adaptation of *Helicobacter pylori*, pp. 947–963

Valeria Montano, Xavier Didelot, Matthieu Foll, Bodo Linz, Richard Reinhardt, Sebastian Suerbaum, Yoshan Moodley, and Jeffrey D. Jensen

Helicobacter pylori is a bacterium that inhabits the stomachs of half of all humans, but the vast majority of infections are asymptomatic. Montano *et al.* analyze the genomes of 60 strains from around the world and find *H. pylori* has been co-habiting with our species much longer than previously thought. The authors demonstrate that this long-term interaction has led to the evolution of differential local adaptation. They also outline the potential for future medical, functional, and evolutionary research on *H. pylori,* our oldest known commensal.

Remarkably divergent regions punctuate the genome assembly of the *Caenorhabditis elegans* Hawaiian strain CB4856, pp. 975–989

Owen A. Thompson, L. Basten Snoek, Harm Nijveen, Mark G. Sterken, Rita J. M. Volkers, Rachel Brenchley, Arjen van't Hof, Roel P. J. Bevers, Andrew R. Cossins, Itai Yanai, Alex Hajnal, Tobias Schmid, Jaryn D. Perkins, David Spencer, Leonid Kruglyak, Erik C. Andersen, Donald G. Moerman, LaDeana W. Hillier, Jan E. Kammenga, and Robert H. Waterston

Thompson *et al.* report a reference genome sequence for the Hawaiian strain CB4856 of *C. elegans*, widely studied for its phenotypic differences from the N2 laboratory strain. This revealed 61 regions spanning 2.8 Mb that contain a disproportionate number of SNVs and an abundance of genes from large, rapidly evolving gene families. Because of their high divergence—up to 16% differences—these regions had largely escaped detection in prior studies. Comparison with other wild isolates suggests that these regions are maintained over long evolutionary periods by balancing selection.

Nonadditive effects of genes in human metabolomics, pp. 707–718

Yakov A. Tsepilov, So-Youn Shin, Nicole Soranzo, Tim D. Spector, Cornelia Prehn, Jerzy Adamski, Gabi Kastenmüller, Rui Wang-Sattler, Konstantin Strauch, Christian Gieger, Yurii S. Aulchenko, and Janina S. Ried

In genome-wide association studies (GWAS) of metabolites, non-additive genetic effects might be especially important because metabolite phenotypes are closer to the underlying pathways than many other traits. However, most GWAS on metabolites assume additivity. Tsepilov *et al.* analyzed a panel of 151 metabolites and their ratios (22,801 in total) for non-additive genetic effects in a population based cohort and found that in fact most SNP effects were additive. This provides empirical support for the additivity of genetic control of metabolism.

Evidence that the origin of naked kernels during maize domestication was caused by a single amino acid substitution in *tga1*, pp. 965–974

Huai Wang, Anthony J. Studer, Qiong Zhao, Robert Meeley, and John F. Doebley

The relative contribution of regulatory and coding changes to the evolution of phenotypic traits is an important, and highly debated, question in evolutionary biology. Wang *et al.* show that a single nucleotide change in the gene *teosinte glume architecture1* (*tga1*) confers naked kernels in maize *vs.* encased kernels in the wild maize progenitor. This polymorphism causes an amino acid substitution in the TGA1 transcriptional regulator, and this affects dimer stability. These results show how morphological evolution can be driven by a simple nucleotide change that alters protein function.

This Month's Perspectives

The "genetic program": behind the genesis of an influential metaphor, pp. 685–696

Alexandre E. Peluffo

"Genetic program" has become a deeply entrenched metaphor which compares organisms to computers executing programs for processes such as reproduction, development, differentiation, apoptosis, homeostasis, and behavior. Based on unpublished archives, Peluffo investigates the genesis of this influential metaphor of the "genetic program," shows how it solved the problem of purpose in biology, and suggests that there was a shared origin for its independent introduction by two articles in 1961, one by French Nobel laureates François Jacob and Jacques Monod and one by prominent American evolutionary biologist Ernst Mayr.

This Month in the American Journal of Human Genetics

The human phenotype ontology: semantic unification of common and rare disease, Am. J. Hum. Gent. 97(1)

Tudor Groza, Sebastian Köhler, Dawid Moldenhauer, Nicole Vasilevsky, Gareth Baynam, Tomasz Zemojtel, Lynn Marie Schriml, Warren Alden Kibbe, Paul N. Schofield, Tim Beck, Drashtti Vasant, Anthony J. Brookes, Andreas Zankl, Nicole L. Washington, Christopher J Mungall, Suzanna E. Lewis, Melissa Haendel, Helen Parkinson, and Peter N. Robinson

The Human Phenotype Ontology (HPO) contains over 11,000 terms describing phenotypes, and has been widely used in the rare disease community to aid in diagnosis and identification of disease-associated candidate genes. In this study, Groza *et al.* expanded the utility of the HPO for common diseases by including information mined from over 5 million PubMed abstracts. As examples of how the HPO can be used, similarities between the networks of phenotypes for diseases were investigated to identify shared underlying etiologies, and overlap between common and rare conditions were identified.