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R/qtl2: software for mapping quantitative trait loci with high-dimensional data and multiparent populations, pp. 495–502

Karl W. Broman, Daniel M. Gatti, Petr Simecek, Nicholas A. Furlotte, Pjotr Prins, Śaunak Sen, Brian S. Yandell, and Gary A. Churchill

R/qtl2 is an interactive software environment for mapping quantitative trait loci (QTL) in experimental populations. The R/qtl2 software expands the scope of the widely-used R/qtl software package to include multi-parental populations, better handles modern high-dimensional data, and includes the ability to perform genome scans using a linear mixed model to account for population structure.

Strategies for efficient genome editing using CRISPR-Cas9, pp. 431–457

Behnom Farboud, Aaron F. Severson, and Barbara J. Meyer

and

Robust CRISPR/Cas9-mediated tissue-specific mutagenesis reveals gene redundancy and perdurance in *Drosophila*, pp. 459–472

Amy R. Poe, Bei Wang, Maria L. Sapar, Hui Ji, Kailyn Li, Tireniolu Onabajo, Rushaniya Fazliyeva, Mary Gibbs, Yue Qiu, Yuzhao Hu, and Chun Han

The CRISPR/Cas9 gene editing system continues to push the boundaries of genetic analysis. Here, papers from Farboud, Severson, and Meyer and Poe *et al*. describe cutting-edge advances for CRISPR use. Farboud, Severson, and Meyer devise a number of strategies in *Caenorhabditis elegans* and other nematode species to maximize the efficiency of genome targeting, lend insight into the timing and mechanism of double-strand break repair, and achieve predictable precise and imprecise repair outcomes with high frequency. Poe *et al*. present an optimized system to achieve highly efficient gene loss of function in a tissue-specific manner in *Drosophila*. They also describe toolkits for making and evaluating enhancer-driven Cas9 and multi-gRNA transgenes.

Evidence for weak selective constraint on human gene expression, pp. 757–772

Emily C. Glassberg, Ziyue Gao, Arbel Harpak, Xun Lan, and Jonathan K. Pritchard

Variation in human complex traits is connected to variation in gene expression, and selection on complex traits can be reflected in selection on gene expression. Here, Glassberg and Gao *et al*. analyze polymorphic gene duplications, expression quantitative trait loci, and allele-specific expression to quantify constraint on expression. They estimate that singletons have greater effects on expression variance than the average variant across allele frequencies and that singletons explain about 5% of the heritability of gene expression attributable to *cis*-regulatory variation. They conclude that constraint on gene expression is present but weak, thus permitting high levels of gene-regulatory genetic variation.

Two antagonistic hippo signaling circuits set the division plane at the medial position in the ciliate *Tetrahymena*, pp. 651–663

Yu-Yang Jiang, Wolfgang Maier, Ralf Baumeister, Ewa Joachimiak, Zheng Ruan, Natarajan Kannan, Diamond Clarke, Panagiota Louka, Mayukh Guha, Joseph Frankel, and Jacek Gaertig

Ciliates divide by tandem duplication, a developmental process that remodels the parental cell into two daughters aligned head-to-tail. Here, Jiang *et al*. investigate the *elo1-1* mutation in *Tetrahymena* that causes the division plan to form too close to the posterior cell end. They show that the ELO1 gene encodes a Lats/NDR kinase of the Hippo signaling cascade that marks the posterior region of the cell cortex, where the division plane does not form in the wild-type. This work reveals that inhibitory influences are an important mode of operation that drives the pattern formation in ciliates.

Joint analysis of multiple interaction parameters in genetic association studies, pp. 483–494

Jihye Kim, Andrey Ziyatdinov, Vincent Laville, Frank B. Hu, Eric Rimm, Peter Kraft, and Hugues Aschard

Despite the extensive literature on methods for assessing interactions between genetic and environmental factors, approaches for the joint analysis of multiple G-E interactions are surprisingly lacking. Kim *et al*. compare the power and robustness of joint analysis approaches for testing multiple interactions jointly in linear and logistic regression using three test statistics: *Wald*, *Score*, and *likelihood ratio test*. They illustrate the relative performances of these approaches through application in three large cohort datasets, including more than 37,000 participants.

Coupling of human rhodopsin to a yeast signaling pathway enables characterization of mutations associated with retinal disease, pp. 597–615

Benjamin M. Scott, Steven K. Chen, Nihar Bhattacharyya, Abdiwahab Y. Moalim, Sergei V. Plotnikov, Elise Heon, Sergio G. Peisajovich, and Belinda S. W. Chang

G protein-coupled receptors (GPCRs) are crucial sensors of extracellular signals in eukaryotes, and direct measurement of GPCR-mediated signaling is useful for high-throughput mutational studies. However, this is particularly difficult for the light-activated GPCR rhodopsin. Here, Scott *et al*. report a fluorescence-based reporter assay in which human rhodopsin is activated in the yeast mating pathway. Their novel yeast-based assay of rhodopsin activation shows similar characteristics as more traditional methods, demonstrating that their engineered yeast strain can be useful in rhodopsin mutant classification that are consistent with clinical phenotypes.

Glucose signaling is connected to chromosome segregation through protein kinase A phosphorylation of the Dam1 kinetochore subunit in *Saccharomyces cerevisiae*, pp. 531–547

Sameer B. Shah, David Parmiter, Christian Constantine, Paul Elizalde, Michael Naldrett, Tatiana S. Karpova, and John S. Choy

Prior studies have suggested a role for the major glucose signaling Ras/Protein Kinase A (PKA) pathway in kinetochore function and chromosome segregation, but with no clear mechanism. Here, Shah *et al*. show that PKA directly phosphorylates Dam1p on an evolutionarily conserved PKA site, thus contributing to the regulation of kinetochore structure and chromosome segregation fidelity. Modulating Ras/PKA activity by reducing glucose levels is associated with changes in phosphorylation of Dam1p. This work provides a mechanism that joins the Ras/PKA pathway to kinetochore function and points to the possibility that chromosome segregation fidelity is influenced by glucose availability.

Cell specificity of human regulatory annotations and their genetic effects on gene expression, pp. 549–562

Arushi Varshney, Hadley VanRenterghem, Peter Orchard, Alan P. Boyle, Michael L. Stitzel, Duygu Ucar, and Stephen C. J. Parker

Varshney *et al*. directly compare five widely-used annotations of active regulatory elements: stretch, super, and typical enhancers; high-occupancy target (HOT) regions; and broad domains in four human cell types. Overall, their results suggest that current expression quantitative trait loci (eQTL) studies are relatively underpowered, potentially lacking the appropriate environmental context to detect genetic effects in the most cell type-specific regulatory annotations and likely contributing to infrequent co-localization of eQTL with genome-wide association study (GWAS) signals.

This Month's Perspectives

Illuminating women's hidden contribution to historical theoretical population genetics

Samantha Dung, Andrea López, Ezequiel Lopez Barragan, Rochelle-Jan Reyes, Ricky Thu, Edgar Castellanos, Francisca Catalan, Emilia Huerta Sanchez, and Rori V. Rohlfs

Through careful review of one eminent journal over the 1970s and 80s, Dung *et al*. found a surprisingly high proportion of the computational work was carried out by women. Consistent with authorship norms of the time, many programmers were only named in acknowledgements, meaning many programmers' names are not widely known or connected with these seminal works. These "acknowledged programmers" were disproportionately women, some of whom performed sophisticated numerical and statistical research. The authors highlight substantial yet historically overlooked contributions women made to theoretical population genetics in the 1970s.