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Estimating tempo and mode of Y chromosome turnover: explaining Y chromosome loss with the fragile Y hypothesis, pp. 561–572

Heath Blackmon and Jeffery P. Demuth

A fundamental question of Y chromosome evolution is whether (or when) the Y will be lost. This study uses beetles, which have over 30 sex chromosome systems, to show that differences in the rate of Y chromosome loss are associated with the meiotic mechanism of XY pairing. The authors propose the "fragile Y" hypothesis, which suggests that taxa are made more prone to aneuploidy by selection to reduce the region of the sex chromosome that recombines. Data from both beetles and mammals were consistent with the predictions of the hypothesis.

Stability and response of polygenic traits to stabilizing selection and mutation, pp. 749–767

Harold P. de Vladar and Nick Barton

Understanding how quantitative traits respond to stabilizing selection is a central question in evolution. The authors show that stabilizing selection leads to a sharp threshold separating allelic effects into two classes, large and small. Quantitative variation is due mostly to alleles of large effect, which remain near fixation. At equilibrium, the mean trait value closely matches the optimum, which can be achieved via alternative allelic combinations. Unlike with equal effects, these alternative fitness peaks are close to the optimum and well connected to each other. Consequently, traits under mutation-selection balance are well adapted, regardless of which peak they have reached.

Predicting discovery rates of genomic features, pp. 601–610

Simon Gravel

For genomic studies of variation, predicting the total number of variants across many samples is useful for optimizing experimental design and understanding the evolution and biology of the samples. The authors show that the number of variable sites can be estimated accurately by sequencing only one out of every twenty samples, independent of the biological or evolutionary source of the variability. They present tractable and robust estimators that can facilitate experimental design by predicting discovery rates as a function of sample composition and size.

Evidence for local regulatory control of escape from imprinted X-chromosome inactivation, pp. 715–723

Joshua W. Mugford, Joshua Starmer, Rex L. Williams, J. Mauro Calabrese, Piotr Mieczkowski, Della Yee, and Terry Magnuson

X-Chromosome Inactivation (XCI) almost completely silences one of two X chromosomes in somatic cells of mammalian females. However, several genes escape XCI by unknown mechanisms. This study tests the conventional hypothesis that particular patterns of chromosomal interactions facilitate escape from imprinted XCI. Contrary to prevailing thought, these results support the hypothesis that regulatory elements in close linear proximity to escaping genes may govern escape from imprinted XCI.

fastSTRUCTURE: variational inference of population structure in large SNP datasets, pp. 573–589

Anil Raj, Mathew Stephens, and Jonathan K. Pritchard

There is an increasing need for fast and accurate tools to infer population structure from very large genetic datasets. This article describes efficient algorithms for approximate inference of the model underlying the STRUCTURE program using a popular framework called variational Bayesian inference. The variational algorithms are almost 100 times faster than STRUCTURE and achieve accuracies comparable to those of ADMIXTURE. The algorithm, fastSTRUCTURE, is freely available online at http://pritchardlab.stanford.edu/structure.html.

Systems genomics of metabolic phenotypes in wild-type *Drosophila melanogaster*, pp. 781–793

Laura K. Reed, Kevin Lee, Zhi Zhang, Lubna Rashid, Any Poe, Benjamin Hsieh, Nigel Deighton, Norm Glassbrook, Rolf Bodmer, and Greg Gibson

Systems biology dissects complex traits in a way that recognizes genetic, physiological and environmental interactions in the generation of phenotypic variation. In this article, transcriptional and metabolic profiling of *Drosophila* across diets showed that genotype-by-diet interactions are a major component of expression variation, but not of metabolomic variation. The authors quantified genomic responses to dietary selection using evolve-and-resequence experiments, finding rapid and replicated changes in gene frequency across hundreds of loci. However, the loci that responded to dietary selection were not those previously identified by functional analyses like differential expression or RNAi screens.

Modeling the zebrafish segmentation clock's gene regulatory network constrained by expression data suggests evolutionary transitions between oscillating and non-oscillating transcription, pp. 725–738

Jamie Schwendinger-Schreck, Yuan Kang, and Scott A. Holley

The segmental pattern of the vertebral column is established during embryogenesis by the segmentation clock. The clock consists of a network of transcriptional repressors that mediate negative autofeedback. Using *in silico* modeling and a global optimization algorithm, this study explores possible clock gene regulatory networks that fit measured transcriptional responses to gene knockdown. The authors discuss the limitations of this methodology and present data suggesting that the zebrafish segmentation clock may have a greater underlying similarity to the amniote equivalent than previously thought.

Domain specificity of MAP3K family members, MLK and Tak1, for JNK signaling in *Drosophila*, pp. 497–513

Beth Stronach, Ashley L. Lennox, and Rebecca A. Garlena

With hundreds of proteins kinases controlling nearly every aspect of cellular behavior, how does a cell specifically activate certain pathways to elicit appropriate responses? This study addresses the question of signaling specificity for two related protein kinases in *Drosophila* by swapping various parts of the proteins and determining the effects in the contexts of development and innate immune response. Even though the enzymes share a common substrate, they are not interchangeable. They reside in different cellular locations, and interactions that are rate limiting in one context are not limiting in all contexts.

This Month's Perspectives

Would Fred Sanger get funded today? pp. 435–439

Stanley Fields

Fred Sanger developed technologies that won him two Nobel Prizes and revolutionized biological research. Yet in spite of this record, the question has been raised as to whether in the current scientific climate he might be unsuccessful in obtaining a grant because of a productivity that would be viewed as too limited. In imagining how an NIH study section today might treat a proposal from Sanger to sequence DNA, we can ask whether there are lessons from his career that suggest changes to the grant review process.

This Month in the American Journal of Human Genetics

Contrasting X-linked and autosomal diversity across 14 human populations, Am. J. Hum. Genet. 94(6)

Leonardo Arbiza, Srikanth Gottipati, Adam Siepel, and Alon Keinan

Differences between the X chromosome and autosomes can provide insights regarding the demographic and selective forces that shaped human history. Previous studies exploring nucleotide diversity on the different chromosomes were limited by sample availability and technology. Arbiza *et al*. analyze over 550 women across 14 populations and find that levels of diversity on the X relative to the autosomes (X/A) are not adequately accounted for by current demographic models, indicating that additional sex-biased demographic processes played an important role in the dispersal of modern humans out of Africa.