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INVESTIGATIONS AND AUTHOR SUMMARIES

- 1061–1068** **Genetic Variants That Confer Resistance to Malaria Are Associated with Red Blood Cell Traits in African-Americans: An Electronic Medical Record-based Genome-Wide Association Study**
Keyue Ding, Mariza de Andrade, Teri A. Manolio, Dana C. Crawford, Laura J. Rasmussen-Torvik, Marylyn D. Ritchie, Joshua C. Denny, Daniel R. Masys, Hayan Jouni, Jennifer A. Pachecho, Abel N. Kho, Dan M. Roden, Rex Chisholm, and Iftikhar J. Kullo
- Using electronic medical records, these authors conducted a genome-wide association study of red blood cell (RBC) traits in 2315 African-Americans. The study revealed three genetic regions associated with at least one RBC trait. These regions contain genes that confer protection against malaria. Regions influencing RBC traits in a European ancestry cohort of similar sample size were not associated with RBC traits in African-Americans. These findings highlight that genetic variants that confer resistance to malaria are associated with RBC traits in African-Americans and suggest that the genetic architecture underlying RBC traits in the two ethnic groups may differ.
- 1069–1083** **Genome-Wide Patterns of Codon Bias Are Shaped by Natural Selection in the Purple Sea Urchin, *Strongylocentrotus purpuratus***
Kord M. Kober and Grant H. Pogson
- These authors are the first to describe genome-wide patterns of codon bias in a marine organism, the purple sea urchin, *Strongylocentrotus purpuratus*. They found that mutational bias has played a minor role in determining codon bias, and translational selection appears to be driving major codon usage. By identifying clusters of genes representing distinct synonymous codon usage, translational selection is attributable to only one group. Preferred major and minor codons are evolutionarily conserved and codon bias may affect mRNA stability. Hence, preferred synonymous codon usage may be heterogeneous across different genes and subject to different forms of natural selection.
- 1085–1093** **Using Genome-Wide Association Analysis to Characterize Environmental Sensitivity of Milk Traits in Dairy Cattle**
Melanie Streit, Robin Wellmann, Friedrich Reinhardt, Georg Thaller, Hans-Peter Piepho, and Jörn Bennewitz
- Genotype-by-environment interaction and environmental sensitivity is a general phenomenon in plant and animal populations. In livestock, breeding for sensitive individuals is an increasingly important issue. Having knowledge about the genetic architecture of environmental sensitivity is essential for breeding purposes. In this article, the authors report the results from a large scale genome-wide association analysis for environmental sensitivity of milk traits in dairy cattle. They were able to detect and confirm several SNP clusters affecting environmental sensitivity. Their results demonstrate that environmental sensitivity is a typical quantitative trait controlled by many genes with small effects and few with larger effects.

- 1095–1104 **How Good Are Indirect Tests at Detecting Recombination in Human mtDNA?**
Daniel James White, David Bryant, and Neil John Gemmell
- Recombination between mitotypes will impact many evolutionary analyses based on mtDNA including phylogenetics, detection of selection, and evolutionary dating. Despite empirical proof of human mtDNA recombination in somatic tissues in 2004 and widespread recombination in animals, plants, and fungi, there remains a lack of irrefutable evidence for human mtDNA recombination at the population-level. These authors hypothesize that recombination is almost assuredly occurring in human and animal mtDNA as it does in plants and fungi but is effectively undetectable except in the most extreme cases. In this study, they explored characteristics specific to human mtDNA sequence that may impact the efficacy of current tests to detect it. Under an evolutionary model that incorporated parameters specific to human mtDNA, tests performed poorly and successful detection rates were limited to a range of 7 to 70%. These results suggest that current tests need further development to reliably detect recombination at the population level in human mtDNA.
- 1105–1114 **Sequence-Based Mapping of the Polyploid Wheat Genome**
Cyrille Sainetnac, Dayou Jiang, Shichen Wang, and Eduard Akhunov
- The emergence of new sequencing technologies has provided fast and cost-efficient strategies for high-resolution mapping of complex genomes. The authors used the wheat iSelect SNP genotyping assay and next-generation sequencing to develop a high-density reference map of the wheat genome. They demonstrate the utility of the assay for gene mapping and ordering shotgun sequence contigs generated from a flow-sorted wheat chromosome. Their reference map includes SSR/STS and DArT markers broadly used in previous gene/QTL mapping projects providing resources to identify a large set of markers linked with the regions of interest and perform high-resolution gene mapping.
- 1115–1127 **The Rate and Effects of Spontaneous Mutation on Fitness Traits in the Social Amoeba, *Dictyostelium discoideum***
David W. Hall, Sara Fox, Jennie J. Kuzdzal-Fick, Joan E. Strassmann, and David C. Queller
- Mutations affecting fitness are of paramount importance in evolution. In this study, the authors estimate the parameters of mutations affecting eight fitness components in the social amoeba, *Dictyostelium discoideum*. Focusing on the rate at which mutations arise, their average effect, and the proportion that are beneficial, the authors found that although *D. discoideum* exhibits one of the lowest base-pair mutation rates ever measured, the rate at which mutations affecting fitness arise is high. This suggests that the molecular basis of fitness-altering mutations does not lie in base pair substitutions, but perhaps in mutations at simple repeat sequences, which are extremely frequent in this species.
- 1129–1141 **Genetic Bypass of *Aspergillus nidulans* *crzA* Function in Calcium Homeostasis**
Ricardo S. Almeida, Omar Loss, Ana Cristina Colabardini, Neil Andrew Brown, Elaine Bignell, Marcela Savoldi, Sergio Pantano, Maria Helena S. Goldman, Herbert N. Arst, Jr, and Gustavo H. Goldman
- In fungi, calcium homeostasis and other calcium-regulated activities are controlled by the transcription factor CrzA. To identify genes that genetically interact with CrzA, the authors selected mutations able to suppress *crzAΔ* calcium intolerance. Through genetic mapping, gene sequencing, and mutant rescue, they identified three genes: *cnaB* (calcineurin regulatory subunit), *folA* (dihydroneopterin aldolase, involved in folic acid biosynthesis), and *scrC* (hypothetical protein). Their results demonstrate that the suppressors conferred calcium tolerance to the *crzAΔ* strain through the restoration of calcium homeostasis. These results suggest that in *Aspergillus nidulans*, calcineurin-dependent and CrzA-independent pathways exist, and CrzA may contribute to folic acid biosynthesis.
- 1143–1149 **A Dynamic Database of Microarray-Characterized Cell Lines with Various Cytogenetic and Genomic Backgrounds**
Zhenya Tang, Dorit S. Berlin, Lorraine Toji, Gokce A. Toruner, Christine Beiswanger, Shashikant Kulkarni, Christa L. Martin, Beverly S. Emanuel, Michael Christman, and Norman P. Gerry
- This article describes a database containing detailed cytogenetic and genomic information for about 900 cell lines collected from individuals representing a variety of disease states, chromosomal abnormalities, heritable diseases, distinct human populations, and apparently healthy individuals. All the information of these cell lines is freely available through several sources, such as the NIGMS Repository website and the UCSC Genome Browser. As additional cell lines are analyzed and subsequently added into it, the database will be maintained dynamically.

- 1151–1163 **Molecular Population Genetics of Inversion Breakpoint Regions in *Drosophila pseudoobscura***
Andre G. Wallace, Don Detweiler, and Stephen W. Schaeffer
- Chromosomal rearrangements can have a profound effect on the pattern and organization of genetic diversity along a chromosome. In this article, the authors examine theoretical predications about how genetic flux between inverted chromosomes alters levels of genetic diversity near and away from chromosomal breakpoint regions in young and old gene arrangements. One important result is that genetic variation in newer chromosomal arrangements does not always have the expected reduced nucleotide polymorphism. This finding supports the idea that genetic exchange is not the sole force that influences genetic variation on inverted chromosomes.
- 1165–1175 **Generalized Admixture Mapping for Complex Traits**
Bin Zhu, Allison E. Ashley-Koch, and David B. Dunson
- Admixture mapping is a popular tool to identify regions of the genome associated with traits in a recently admixed population. Despite its popularity, the applications are limited by the analysis methods. Existing methods have been developed primarily for identification of a single locus influencing a dichotomous trait within a case-control study design. In this article, the authors propose a generalized admixture mapping (GLEAM) approach, a flexible and powerful regression method for both quantitative and qualitative traits that is able to test for association between the trait and local ancestries in multiple loci simultaneously and performs well in both the simulation study and real data analysis.
- 1177–1189 **Spatial Profiling of Nuclear Receptor Transcription Patterns over the Course of *Drosophila* Development**
Ronit Wilk, Jack Hu, and Henry M. Krause
- Nuclear receptors coordinate processes such as feeding, development, and reproduction with metabolism. In this article, the authors use high-resolution fluorescence *in situ* hybridization to track the spatial expression patterns of all 18 *Drosophila* nuclear receptors over the entire course of embryogenesis, and in all tissues of wandering 3rd instar larva. In addition to tissues involved in metabolite uptake, storage, and elimination, other sites of expression included tissues involved in vision, immunity, and behavior. Surprisingly, all 18 mRNAs also exhibited striking subcellular distributions. These tissue and subcellular expression patterns provide many new insights into nuclear receptor regulation, functions, and interactions.
- 1191–1194 **The Evolution of the *Anopheles* 16 Genomes Project**
Daniel E. Neafsey, George K. Christophides, Frank H. Collins, Scott J. Emrich, Michael C. Fontaine, William Gelbart, Matthew W. Hahn, Paul I. Howell, Fotis C. Kafatos, Daniel Lawson, Marc A. T. Muskavitch, Robert M. Waterhouse, Louise J. Williams, and Nora J. Besansky
- These authors report the imminent completion of a set of reference genome assemblies for 16 species of *Anopheles* mosquitoes. These genome sequences will greatly facilitate exploration of the capacity exhibited by some *Anopheline* mosquito species to serve as vectors for malaria parasites. A community analysis project will commence soon to perform a thorough comparative genomic investigation of these newly sequenced genomes. Completion of this project using short next generation sequence reads required innovation in both the bioinformatic and laboratory realms. The resulting knowledge gained could prove useful for genome sequencing projects targeting other unconventional genomes.
- 1195–1201 **Major Histocompatibility Complex Class I Haplotype Diversity in Chinese Rhesus Macaques**
Julie A. Karl, Patrick S. Bohn, Roger W. Wiseman, Francesca A. Nimityongskul, Simon M. Lank, Gabriel J. Starrett, and David H. O'Connor
- In this article, the authors describe transcript-based major histocompatibility complex (MHC) class I haplotypes in Chinese rhesus macaques, an under-characterized macaque population used to model human infectious diseases. They define a method for concise reporting of the full complement of major MHC class I alleles expressed by each macaque. Their study also identified common ancestral haplotypes shared with Indian rhesus macaques, which may facilitate improved CD8+ T-cell immunology studies in nonhuman primates.