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- 157–165 **Genetic Analysis of Hematological Parameters in Incipient Lines of the Collaborative Cross**  
*Samir N. P. Kelada, David L. Aylor, Bailey C. E. Peck, Joseph F. Ryan, Urraca Tavarez, Ryan J. Buus, Darla R. Miller, Elissa J. Chesler, David W. Threadgill, Gary A. Churchill, Fernando Pardo-Manuel de Villena, and Francis S. Collins*

Hematological parameters such as red and white blood cell counts are widely used clinical indicators of health, and vary based on genetic factors. We used a newly developed mouse resource, the Collaborative Cross (CC), to identify regions of the genome associated with variation in mean red blood cell volume, white blood cell count, and the relative proportions of white blood cell types. Using evolutionary principles and unique bioinformatics resources, the authors define narrow candidate regions and propose a small number of genes for future studies.

- 167–174 **Genome-Wide Association Mapping of Quantitative Traits in Outbred Mice**  
*Weidong Zhang, Ron Korstanje, Jill Thaisz, Frank Staedtler, Nicole Harttman, Lingfei Xu, Minjie Feng, Liane Yanas, Hyuna Yang, William Valdar, Gary A. Churchill, and Keith DiPetrillo*

The developments in genotyping and analysis methods that have enabled human genome-wide association (GWA) studies can also be applied to outbred mouse populations, which are expected to provide high mapping resolution. We performed GWA mapping using 288 outbred NMRI mice genotyped with a high-density SNP array to map loci influencing five cardiovascular phenotypes. We found significant associations with HDL cholesterol and suggestive associations with the other traits. Additionally, our analysis illustrates the utility of multi-locus modeling in association mapping, whereby the analytical methods described here could be applied to genome-wide association studies for both mice and humans.

- 175–189 **HTreeQA: Using Semi-Perfect Phylogeny Trees in Quantitative Trait Loci Study on Genotype Data**  
*Zhaojun Zhang, Xiang Zhang, and Wei Wang*

Collaborative Cross (CC) is an emerging resource for studying mammalian system genetics, and offers rich genetic and phenotypic diversity. How do we benefit from the unique genomic architecture of the CC population in understanding the roles of genetic variation in complex traits? Traditional phylogeny-based methods cannot be directly applied on the incipient CC strains because of remaining heterozygosity. Can we overcome this barrier? We answer these two questions by a novel method for quantitative trait loci (QTL) study which delivers promising results.

- 191–198 **Accelerating the Inbreeding of Multi-Parental Recombinant Inbred Lines Generated By Sibling Matings**  
*Catherine E. Welsh and Leonard McMillan*
- Generating inbred lines is a costly undertaking requiring, at a minimum, 20 successive generations of sibling matings where a majority of line starts fail. Using simulations, we explored several alternative breeder-selection methods. For each approach we simulated 100,000 independent lines to estimate distributions of generations to achieve full-fixation, as well as to achieve a mean heterozygosity level equal to 20 generations of randomized sib-mating. Our analyses suggest that the number of generations to fully-inbred status can be significantly reduced with minimal impact on the number of haplotype segments.
- 199–202 **Haplotype Probabilities in Advanced Intercross Populations**  
*Karl W. Broman*
- Because of the accumulation of recombination events across the multiple generations, advanced intercross populations have the advantage of greater precision of genetic mapping. Related designs include heterogeneous stock and the diversity outcross population. I derive the two-locus haplotype probabilities on the autosome and X chromosome with these designs. Such probabilities are important ingredients for the treatment of missing genotype information in QTL mapping.
- 203–211 **Transcriptome Atlases of Mouse Brain Reveals Differential Expression Across Brain Regions and Genetic Backgrounds**  
*Wei Sun, Seunggeun Lee, Vasyl Zhabotynsky, Fei Zou, Fred A. Wright, James J. Crowley, Zaining Yun, Ryan J. Buus, Darla R. Miller, Jeremy Wang, Leonard McMillan, Fernando Pardo-Manuel de Villena, and Patrick F. Sullivan*
- We demonstrated that whole brain and forebrain have similar gene expression profiles and exhibit similar responses to genetic perturbations. We identified several functional categories that response to the acute clozapine exposure. We found that transcripts with stronger strain effects were more likely to be located in genomic regions that were not identical-by-descent (IBD) between strains.
- 213–221 **Expression Quantitative Trait Loci for Extreme Host Response to Influenza A in Pre-Collaborative Cross Mice**  
*Daniel Bottomly, Martin T. Ferris, Lauri D. Aicher, Elizabeth Rosenzweig, Alan Whitmore, David L. Aylor, Bart L. Haagmans, Lisa E. Gralinski, Birgit G. Bradel-Tretheway, Janine T. Bryan, David W. Threadgill, Fernando Pardo-Manuel de Villena, Ralph S. Baric, Michael G. Katze, Mark Heise, and Shannon K. McWeeney*
- This is the first systems-level genetics study of influenza in a complex mouse model (where the level of genetic diversity approximates that seen in human populations). In addition to carrying out a very focused eQTL scan, we also developed unbiased methods for determining allele groups and validating the predicted allele effects using qPCR as well as extending the use of local structural equation models to complex crosses. This work provides the initial framework for identifying causal variants and elucidating of the underlying biological sub-networks involved in response to infectious disease.
- INVESTIGATIONS**
- 223–233 **A Resource of Quantitative Functional Annotation for *Homo sapiens* Genes**  
*Murat Taşan, Harold J. Drabkin, John E. Beaver, Hon Nian Chua, Julie Dunham, Weidong Tian, Judith A. Blake, and Frederick P. Roth*
- We integrate a diverse collection of genome-wide and unbiased data to make quantitative function predictions for nearly all genes in the human genome. All predictions are made available through a publicly accessible website, allowing researchers to rapidly gain an understanding of their gene of interest, without having to mine through the various genomic databases.
- 235–248 **Extent With Modification: Leg Patterning in the Beetle *Tribolium castaneum* and the Evolution of Serial Homologs**  
*David R. Angelini, Frank W. Smith, and Elizabeth L. Jockusch*
- Serial homologs are similar structures that develop at different positions within a body plan. Their evolution is thought to be constrained by shared gene functions. Through functional analyses of 17 genes during metamorphic development of the legs in *Tribolium castaneum*, this study compares embryonic and adult leg development, leg patterning among insect species, and between the development of serially homologous appendages. Despite anatomical conservation of insect legs, several differences in gene function are identified. In comparing appendage types across insect species, we highlight the prevalence of pleiotropic changes affecting serial homologs during the diversification of insects.

- 249–260 **A Whole-Chromosome Analysis of Meiotic Recombination in *Drosophila melanogaster***  
*Danny E. Miller, Satomi Takeo, Kavyasree Nandan, Ariel Paulson, Madelaine M. Gogol, Aaron C. Noll, Anoja G. Perera, Kendra N. Walton, William D. Gilliland, Hua Li, Karen K. Staehling, Justin P. Blumenstiel, and R. Scott Hawley*
- In sexually reproducing species, genetic recombination during meiosis plays an important role in determining the evolutionary fate of beneficial mutations and ensuring proper chromosome segregation. A failure in the machinery of meiotic recombination can lead to chromosomal non-disjunction events that can have a tremendous impact on human health. In spite of great importance, very little is known about how patterns of meiotic recombination are established across the genome. Here, using a whole genome sequencing approach, we provide a new view of the landscape of meiotic recombination in *Drosophila*.
- 261–270 **Whole-Genome Sequencing of *Sordaria macrospora* Mutants Identifies Developmental Genes**  
*Minou Nowrousian, Ines Teichert, Sandra Masloff, and Ulrich Kück*
- Recently, the advent of next-generation sequencing techniques has made it possible to identify mutations responsible for mutant phenotypes by whole-genome sequencing of mutants. However, most studies have been restricted to model organisms, where available physical mapping data can aid the bioinformatics analyses. Here, we describe a mutant sequencing approach for a fungus without prior mapping data. We sequenced three mutant strains of *Sordaria macrospora* and identified the causative mutations through bioinformatics analysis. In all cases, transformation with a wild type-copy of the affected gene complemented the mutant, demonstrating the validity of this whole-genome sequencing approach to detect causative mutations.
- 271–278 **Narrowing Down the Mapping of Plant Sex-Determination Regions Using New Y-Chromosome-Specific Markers and Heavy-Ion Beam Irradiation-Induced Y-Deletion Mutants in *Silene latifolia***  
*Naoko Fujita, Chihiro Torii, Kotaro Ishii, Wataru Aonuma, Yuji Shimizu, Yusuke Kazama, Tomoko Abe, and Shigeyuki Kawano*
- We developed seventeen new mutants induced by the advanced technology, heavy-ion beam irradiation, and six new Y chromosome specific markers in the dioecious plant *Silene latifolia*, which has long been a model species for plant sex chromosome research. Because its X and Y chromosomes are extraordinarily large, new Y-specific markers and generated Y deletion mutants were efficient resources to narrow down the genetic map of sex determination region of the Y chromosome. This study is a meaningful step toward understanding the structure and organization of *S. latifolia* Y chromosome.
- 279–286 **Correlation of Global MicroRNA Expression With Basal Cell Carcinoma Subtype**  
*Christopher Heffelfinger, Zhengqing Ouyang, Anna Engberg, David J. Leffell, Allison M. Hanlon, Patricia B. Gordon, Wei Zheng, Hongyu Zhao, Michael P. Snyder, and Allen E. Bale*
- Basal cell carcinomas (BCCs) are the most common cancers in the United States. Several subtypes are distinguished by histology and biologic behavior. In this study, global miRNA expression was examined by sequencing in eight infiltrative BCCs, which are aggressive tumors, and eight nodular BCCs, an indolent subtype. Principal components analysis correctly classified the infiltrative tumors on the basis of miRNA expression. Nodular tumors did not cluster tightly, likely reflecting broader diversity in this class. qPCR validated results of sequencing in a replication set of four infiltrative and three nodular tumors. These results, representing the first miRNA study in BCCs, demonstrate a role for miRNA in tumor pathogenesis.
- 287–297 **Physical and Linkage Maps for *Drosophila serrata*, a Model Species for Studies of Clinal Adaptation and Sexual Selection**  
*Ann J. Stocker, Bosco B. Rusuwa, Mark J. Blacket, Francesca D. Frentiu, Mitchell Sullivan, Bradley R. Foley, Scott Beatson, Ary A. Hoffmann, and Stephen F. Chenoweth*
- The fruit fly *Drosophila serrata* is a member of the *montium* group, a large group of drosophilids consisting of an estimated 98 species. Genomic resources are limited for *D. serrata* despite its use as a model species for evolutionary studies of climatic adaptation and sexual selection. Here, we provide physical and first-generation linkage maps for this species that can be used to guide future genome assembly efforts and QTL mapping studies.

299–311 ***Pichia sorbitophila*, an Interspecies Yeast Hybrid, Reveals Early Steps of Genome Resolution After Polyploidization**

Véronique Leh Louis, Laurence Despons, Anne Friedrich, Tiphaine Martin, Pascal Durrens, Serge Casarégola, Cécile Neuvéglise, Cécile Fairhead, Christian Marck, José A. Cruz, Marie-Laure Straub, Valérie Kugler, Christine Sacerdot, Zlatyo Uzunov, Agnes Thierry, Stéphanie Weiss, Claudine Bleykasten, Jacky De Montigny, Noemie Jacques, Paul Jung, Marc Lemaire, Sandrine Mallet, Guillaume Morel, Guy-Franck Richard, Anasua Sarkar, Guilhem Savel, Joseph Schacherer, Marie-Line Seret, Emmanuel Talla, Gaelle Samson, Claire Jubin, Julie Poulain, Benoît Vacherie, Valérie Barbe, Eric Pelletier, David J. Sherman, Eric Westhof, Jean Weissenbach, Philippe V. Baret, Patrick Wincker, Claude Gaillardin, Bernard Dujon, and Jean-Luc Souciet

The molecular characterization of yeast hybrid genomes remains limited, if one excepts those of the *Saccharomycetaceae* species. This article goes beyond the description of an hybrid yeast genome by providing a detailed analysis of the evolutionary history of the hybrid *Pichia sorbitophila*, a member of the “CTG” group of the *Saccharomycotina*. We characterize the genomic changes that occurred since the separation of the two progenitors of *P. sorbitophila* from their common ancestor, until the *P. sorbitophila* hybrid formation and its recent evolution. We describe also the physiological characteristics of *P. sorbitophila* determined by unequal contributions of its two parents.

313–321 **Evolution of a Large, Conserved, and Syntenic Gene Family in Insects**

Neethu Shah, Douglas R. Dorer, Etsuko N. Moriyama, and Alan C. Christensen

This article reveals that the *Osiris* gene family, previously described in *Drosophila* and *Anopheles* species, is conserved across a wide range of insects, and has been maintained in nearly perfect synteny at least since the divergence of the hemi- and holometabolous insects, and likely longer.

**RELATED ARTICLES IN GENETICS:**

**The Genome Architecture of the Collaborative Cross Mouse Genetic Reference Population**

*Collaborative Cross Consortium*

Genetics 190: 389–401.

**Genotype Probabilities at Intermediate Generations in the Construction of Recombinant Inbred Lines**

*Karl W. Broman*

Genetics 190: 403–412.

**A General Bayesian Approach to Analyzing Diallel Crosses of Inbred Strains**

*Alan B. Lenarcic, Karen L. Svenson, Gary A. Churchill, and William Valdar*

Genetics 190: 413–435.

**High-Resolution Genetic Mapping Using the Mouse Diversity Outbred Population**

*Karen L. Svenson, Daniel M. Gatti, William Valdar, Catherine E. Welsh, Ryan Cheng, Elissa J. Chesler, Abraham A. Palmer, Leonard McMillan, and Gary A. Churchill.*

Genetics 190: 437–447.

**Imputation of Single-Nucleotide Polymorphisms in Inbred Mice Using Local Phylogeny**

*Jeremy R. Wang, Fernando Pardo-Manuel de Villena, Heather A. Lawson, James M. Cheverud, Gary A. Churchill, and Leonard McMillan*

Genetics 190: 449–458.

**Quantitative Trait Loci Association Mapping by Imputation of Strain Origins in Multifounder Crosses**

*Jin J. Zhou, Anatole Ghazalpour, Eric M. Sobel, Janet S. Sinsheimer, and Kenneth Lange*

Genetics 190: 459–473.

**Varying Coefficient Models for Mapping Quantitative Trait Loci Using Recombinant Inbred Intercrosses**

*Yi Gong and Fei Zou*

Genetics 190: 475–486.