ISSUE HIGHLIGHTS

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Regulation of sex determination in mice by a non-coding genomic region, pp. 885–897

Valerie A. Arboleda, Alice Fleming, Hayk Barseghyan, Emmanuèle Délot, Janet S. Sinsheimer, and Eric Vilain

Mice with autosomes and an X-chromosome from C57BL/6J (B6) and a Y-chromosome from the wild-derived *M.m. domesticus poschiavinus* strain, called (B6-Y^{POS}), show XY-sex reversal and female phenotype. This article shows that through congenic breeding, a small 1.62 Mb congenic region derived from the *POSA* semi-inbred strain located in the regulatory region of the *Sox9* results in protection from XY-sex reversal and fertility through regulation of *Sox9* gene expression.

Whole exome sequencing of distant relatives in multiplex families implicates rare variants in candidate genes for oral clefts, pp. 1039–1044

Alexandre Bureau, Margaret M. Parker, Ingo Ruczinski, Margaret A. Taub, Mary L. Marazita, Jeffrey C. Murray, Elisabeth Mangold, Markus M. Noethen, Kirsten U. Ludwig, Jacqueline B. Hetmanski, Joan E. Bailey-Wilson, Cheryl D. Cropp, Qing Li, Silke Szymczak, Hasan Albacha-Hejazi, Khalid Alqosayer, L. Leigh Field, Yah-Huei Wu-Chou, Kimberly F. Doheny, Hua Ling, Alan F. Scott, and Terri H. Beaty

Oral clefts are common craniofacial malformations with both environmental and genetic risk factors. However, few causal variants have been identified. Whole exome sequencing was used to identify causal rare variants shared by distant relatives drawn from 55 multiplex cleft families. From 348 candidate genes, five novel and potentially damaging SNVs shared by affected distant relatives were identified. One, in CDH1, attained statistical significance and was shared by three affected second cousins. Using family based designs in whole exome sequencing studies offers important advantages for understanding complex and heterogeneous disorders.

How to infer relative fitness from a sample of genomic sequences, pp. 913–923

Adel Dayarian and Boris I. Shraiman

Genealogical trees for populations under selection are quantifiably different from those expected under neutral evolution. Here, the authors demonstrate that under certain conditions, a tree reconstructed from a population sample of genomes contains enough information to infer their approximate fitness ranking. This makes it possible to predict which branches of the genealogy are likely to give rise to future generations. The authors propose that the approach could be used for inferring relative fitness of genomes obtained in single-cell sequencing of tumors and in monitoring viral outbreaks.

Sex-biased gene expression and evolution of the X chromosome in nematodes, pp. 865–883

Sarah Elizabeth Albritton, Anna-Lena Kranz, Prashant Rao, Maxwell Kramer, Christoph Dieterich, and Sevinç Ercan

Genes that are differentially expressed between sexes are not randomly distributed between the X and autosomes. Here, the authors analyzed X chromosome evolution and sex-biased gene expression in five nematode species. Nematode X is enriched for genes with high female-biased expression, and depleted for genes with high male-biased expression in the gonad. As predicted by Ohno's hypothesis of X-upregulation, overall transcript levels from the X and autosomes are similar. However, differentially located orthologs show lower expression from the X chromosome than autosomes, suggesting that X-upregulation does not act on every gene.

Effect of domestication on the spread of the [PIN+] prion in *Saccharomyces cerevisiae*, pp. 1007–1024

Amy C. Kelly, Ben Busby, and Reed B. Wickner

Yeast prions are infectious proteins that can propagate vertically to offspring and spread horizontally by outcross mating. This study of 75 wild strains showed that the 15 that carry the [PIN+] prion are largely commercial baking and brewing strains, whereas [PIN+] was not found in ancestral isolates. The commercial strains also show the strongest evidence of past out-cross mating. The association of more frequent outcross mating with [PIN+] suggests that this prion is a sexually transmitted infectious condition.

Bypassing the requirement for an essential MYST acetyltransferase, pp. 851–863

Ana Lilia Torres-Machorro and Lorraine Pillus

Like its cancer-associated human homolog Tip60, yeast Esa1 is an essential MYST family histone acetyltransferase. For the past 15 years, study of *ESA1* was limited to conditional alleles. The authors discovered circumstances that allow cells to live without *ESA1* and conclude that the essential function of the protein is to maintain an overall balance of acetylation in the cell by acting in conjunction with other chromatin modifiers. They also uncovered specific functional interactions that promote viability, stress response and repair of DNA damage.

Pleiotropic mutations are subject to strong stabilizing selection, pp. 1051–1062

Katrina McGuigan, Julie M. Collet, Scott L. Allen, Stephen F. Chenoweth, and Mark W. Blows

An important premise in models of evolution is that mutations with broad pleiotropic effects are under stronger purifying (stabilizing) selection than mutations with more limited effects, but evidence in support of this assumption is limited. The authors assay an outbred population and mutation accumulation lines to estimate the selection coefficients (s) of gene expression traits in male *Drosophila serrata*. The s for pleiotropic combinations of expression traits were three times larger than s of the individual constituent traits, demonstrating that, as expected, stabilizing selection is stronger on more pleiotropic mutations.

A Bayesian approach to inferring the phylogenetic structure of communities from metagenomic data, pp. 925–937

John D. O'Brien, Xavier Didelot, Zamin Iqbal, Lucas Amenga-Etego, Bartu Ahiska, and Daniel Falush

Metagenomics provides a powerful new tool for investigating evolutionary interactions with the environment. However, an absence of model-based statistical methods means that researchers are often not able to make full use of this complex information. The authors present a Bayesian method for inferring the phylogenetic relationship among related organisms found within metagenomic samples. The approach exploits variation in the frequency of taxa among samples to simultaneously infer each lineage haplotype, the phylogenetic tree connecting them, and their frequency within each sample.

This Month's Perspectives

The "domestication syndrome" in mammals: a unified explanation based on neural crest cell behavior and genetics, pp. 795–808

Adam S. Wilkins, Richard W. Wrangham, and W. Tecumseh Fitch

The domestication of mammals is accompanied by the development of a diverse suite of traits, including morphological and physiological features as well as behavioral ones. This "domestication syndrome" was first discovered by Darwin in 1868, an inadvertent by-product of his search for a mechanism of heredity, and has remained a puzzle ever since. In this article, it is proposed that it is a polygenic condition involving mild loss-of-function mutations affecting the neural crest cells. The genetic evidence is evaluated and experimental tests are proposed.

This Month in the American Journal of Human Genetics

Gene-Age Interactions in Blood Pressure Regulation: A Large-Scale Investigation Using the CHARGE, Global BPgen, and ICBP Consortia, Am. J. Hum. Genet. 95(1)

Jeannette Simino, Gang Shi, Joshua C. Bis, Daniel I. Chasman, Georg B. Ehret, et al.

Elevated blood pressure is a well-known risk factor for heart attack, stroke, and metabolic syndrome, and much effort is devoted to prevention, detection, and treatment of hypertension. Although age is known to play a large role in cardiovascular health, the interplay between age and the genetic architecture of blood pressure regulation has remained largely unexplored. Now, by developing methods to address this question, Simino *et al*. are able to identify loci that exhibit age-dependent effects on blood pressure. These findings should provide insight into the biology that underlies blood pressure regulation in different age groups, perhaps aiding in the development of new treatment strategies.