

Functional divergence of the nuclear receptor *NR2C1* as a modulator of pluripotentiality during hominid evolution, pp. 905–922

Jennifer L. Baker, Katherine A. Dunn, Joseph Mingrone, Bernard A. Wood, Beverly A. Karpinski, Chet C. Sherwood, Derek E. Wildman, Thomas M. Maynard, and Joseph P. Bielawski

To investigate the role of nuclear receptors (NRs) in hominid evolution, Baker *et al.* analyzed selection on all 48 human NRs. They identified *NR2C1* as a candidate for contributing to the development of large primate brains. To evaluate this hypothesis, they inferred the sequence of *NR2C1* for the ancestor of human and chimpanzees, and synthesized and expressed the ancestral protein in the laboratory. Functional comparison of the ancestral and modern proteins indicate they differ in several aspects of stem cell regulation affecting neuronal differentiation. The authors propose that *NR2C1* could be associated with characteristics that distinguish humans from the other great apes.

Cross-talk between sporophyte and gametophyte generations is promoted by CHD3 chromatin remodelers in *Arabidopsis thaliana*, pp. 817–829

Benjamin Carter, James T. Henderson, Elisabeth Svedin, Martijn Fiers, Kyle McCarthy, Amanda Smith, Changhua Guo, Brett Bishop, Heng Zhang, Tjitske Riksen, Allison Shockley, Brian P. Dilkes, Kim Boutilier, and Joe Ogas

The developmental complexity of multicellular organisms can obscure whether phenotypes resulting from loss of a ubiquitous regulator reflect the role of that factor in every tissue or only one. Carter *et al.* demonstrate that multiple reproductive defects associated with loss of a CHD chromatin remodeler in *Arabidopsis* result from loss in a distinct compartment, the maternal sporophyte. They also reveal opposing roles for two CHD remodelers in determining seed size, which acts as a novel trans-generational determinant of developmental identity in seedlings. These analyses illustrate the importance of considering non-autonomous mechanisms when investigating the contribution of an epigenetic regulator to a complex developmental process.

Evolution of schooling behavior in threespine sticklebacks is shaped by the *Eda* gene, pp. 677–681

Anna K. Greenwood, Margaret G. Mills, Abigail R. Wark, Sophie L. Archambeault, and Catherine L. Peichel

Greenwood *et al.* used transgenic approaches to show that natural variation in schooling behavior between two populations of threespine sticklebacks is caused by the gene *Ectodysplasin*. This work provides a rare example of a genetic change that underlies the evolution of vertebrate behavior in the wild.

The genetic cost of Neanderthal introgression, pp. 881–891

Kelley Harris and Rasmus Nielsen

Previous studies have shown that Neanderthals were inbred compared to humans, and also that Neanderthals interbred with the ancestors of people living outside Africa today, contributing 1 to 4% of their modern gene pool. We use simulations to show that Neanderthal inbreeding likely caused accumulation of harmful mutations, and they may have had 40% lower fitness than humans. Many of these harmful mutations are predicted to persist in modern human populations, although most have been eliminated by natural selection in humans since the time of interbreeding.

Unexpected roles for ciliary kinesins and intraflagellar transport proteins, pp. 771–785

Niedharsan Pooranachandran and Jarema J. Malicki

Cilia are essential for the function of sensory organs throughout the animal kingdom. Cilia formation and function depends on kinesin 2 family motors and on intraflagellar transport (IFT) proteins, which mediate transport inside the ciliary shaft. The authors show that both the main ciliary motor (heterotrimeric kinesin 2) and IFT proteins display unexpected functions in zebrafish photoreceptors, suggesting a much broader role than previously assumed. These functions are essential for photoreceptor cilia formation and photoreceptor survival. Surprisingly, however, sensory cristae in the ear do not require this motor for some aspects of ciliogenesis and the homodimeric kinesin 2 is not necessary for cilia morphogenesis in all tissues examined thus far.

Efficient genome-wide sequencing and low-coverage pedigree analysis from noninvasively collected samples, pp. 699–714

Noah Snyder-Mackler, William H. Majoros, Michael L. Yuan, Amanda O. Shaver, Jacob B. Gordon, Gisela H. Kopp, Stephen A. Schlebusch, Jeffrey D. Wall, Susan C. Alberts, Sayan Mukherjee, Xiang Zhou, and Jenny Tung

Methods for genotyping non-invasively collected samples have remained largely unchanged for the past 20 years. Snyder-Mackler *et al.* developed an efficient protocol for genome-wide capture of endogenous DNA from non-invasively collected samples and coupled it with a computational approach to reconstruct pedigree links. The enrichment method increased endogenous DNA up to 40-fold, and the computational approach reconstructed near-perfect pedigree relationships even with extremely low-coverage sequencing. These methods will enable research on natural populations to again take a major leap forward, into the genomic era.

Transcript isoform variation associated with cytosine modification in human lymphoblastoid cell lines, pp. 985–995

Xu Zhang and Wei Zhang

Natural variation of DNA methylation and its correlation with gene expression variation has been extensively studied. The extent of correlation between DNA methylation and alternative transcript isoforms among individuals and the underlying mechanisms, however, remain unclear. This study explored these aspects using genome-wide data derived from human lymphoblastoid cell lines from unrelated individuals. The study demonstrated a prominent effect of cytosine modification variation on transcript isoform spectrum over gross transcript abundance, and revealed epigenetic contributions to diseases that were mediated through cytosine modification-specific TTV.

Accurate profiling of gene expression and alternative polyadenylation with whole transcriptome termini site sequencing (WTTS-Seq), pp. 683–697

Xiang Zhou, Rui Li, Jennifer J. Michal, Xiao-Lin Wu, Zhongzhen Liu, Hui Zhao, Yin Xia, Weiwei Du, Mark R. Wildung, Derek J. Pouchnik, Richard M. Harland, and Zhihua Jiang

Construction of next-generation sequencing (NGS) libraries for transcriptome analysis involves RNA manipulation, which contributes to noisy, biased, and artifactual data. To minimize such problems, Zhou *et al.* developed a whole transcriptome termini site sequencing (WTTS-seq) method which enriches both polyA+ RNA and cDNA, adds 5' and 3' adaptors in one step, pursues strand sequencing, and profiles both gene expression and alternative polyadenylation (APA). The technique can also detect shorter transcripts and reduce false discovery of differentially expressed genes.

This Month in the American Journal of Human Genetics**RNA interference prevents autosomal dominant hearing loss, Am. J. Hum. Genet. 98(6)**

Seiji B. Shibata, Paul T. Ranum, Hideaki Moteki, Bifeng Pan, Alexander T. Goodwin, Shawn S. Goodman, Paul J. Abbas, Jeffrey R. Holt, and Richard J. H. Smith

Hearing impairment affects over 300 million people worldwide. Although treatment options such as hearing aids and cochlear implants can improve quality of life, they are unable to restore normal hearing. Because hearing loss often results from dominant gain-of-function mutations, targeting of the mutant allele, while maintaining the function of the normal allele, could potentially mitigate or prevent hearing loss. Shibata *et al.* demonstrate that a single intracochlear injection of an artificial microRNA can slow the progression of hearing loss in a mouse model of autosomal dominant hearing loss. Technical hurdles will need to be addressed before such an approach is feasible in humans, but this study suggests that many cases of hearing loss could be amenable to miRNA-mediated gene therapy.