

## ISSUE HIGHLIGHTS

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### Neuronal remodeling during metamorphosis is regulated by the *alan shepard (shep)* gene in *Drosophila melanogaster*, pp. 1267–1283

Dahong Chen, Chunjing Qu, and Randall S. Hewes

The ability of mature nerve cells to reestablish connections following damage is limited. Nevertheless, mature nerve cells can undergo substantial morphological remodeling in certain situations. To identify factors controlling development of peptidergic neurons, the authors performed a screen of *Drosophila melanogaster* splice-trap lines. The SHEP protein was found to play an important role in the metamorphosis-specific growth of diverse neurons and is closely related to a human MSSP DNA/RNA binding protein.

### Dating rare mutations from small samples with dense marker data, pp. 1315–1327

Luke C. Gandolfo, Melanie Bahlo, and Terence P. Speed

Many questions in evolution and natural history require estimating the age of mutations. Methods for dating mutations have two major limitations: they cannot be applied reliably in situations involving rare mutations, where sample sizes are typically small, and they cannot make effective use of modern high-density SNP data. Here, the authors describe a method that overcomes these problems and has other advantages over existing methods.

### A co-CRISPR strategy for efficient genome editing in *Caenorhabditis elegans*, pp. 1069–1080

Heesun Kim, Takao Ishidate, Krishna S. Ghanta, Meetu Seth, Darryl Conte Jr., Masaki Shirayama, and Craig C. Mello

This article reports improvements to the efficiency of CRISPR-Cas9 genome editing in *Caenorhabditis elegans*, including methods for detecting homologous recombination (HR) events and a co-CRISPR strategy to facilitate both sgRNA selection and recovery of homologous events. The authors find that HR efficiencies using CRISPR are remarkably high, making it possible to precisely edit the *Caenorhabditis elegans* genome without selection.

### Insights into three whole-genome duplications gleaned from the *Paramecium caudatum* genome sequence, pp. 1417–1428

Casey L. McGrath, Jean-Francois Gout, Thomas G. Doak, Akira Yanagi, and Michael Lynch

Whole-genome duplications (WGDs) have occurred recurrently in the history of eukaryotes, yet the evolutionary mechanisms governing the retention or loss of duplicated genes are poorly understood. *Paramecium aurelia* is a complex of species that share at least three successive WGDs. Here, the authors report the genome sequence of *Paramecium caudatum* and show that it diverged from the *aurelias* before the two most recent WGDs. From the most ancient WGD (the only one shared between *Paramecium caudatum* and the *aurelias*), *Paramecium caudatum* maintains twice as many paralogs as *P. aurelia*, suggesting that paralog retention is influenced by subsequent WGDs. The probability of post-WGD survival of duplicates was also influenced by GC content and expression level.

### A powerful and adaptive association test for rare variants, pp. 1081–1095

Wei Pan, Junghi Kim, Yiwei Zhang, Xiaotong Shen, and Peng Wei

With increasing interest in detecting associations between complex traits and rare variants (RVs), many new statistical tests have been proposed. However, the relative performance of these tests, especially in the presence of many non-associated variants, is largely unknown. These authors show that several representative tests, including SKAT and SKAT-O, do not perform well in the presence of many non-associated single nucleotide variants. They propose a highly adaptive test that remains competitive across a wide range of scenarios and has the potential to be useful not only for rare variants, but also common ones.

### Genome properties and prospects of genomic prediction of hybrid performance in a breeding program of maize, pp. 1343–1355

Frank Technow, Tobias A. Schrag, Wolfgang Schipprack, Eva Bauer, Henner Simianer, and Albrecht E. Melchinger

Heterosis, or hybrid vigor, plays an important role in crop breeding. To test the prospects of genomic prediction of hybrid performance in maize – a model species for heterosis research – the authors analyzed genomic and phenotypic data from 1,254 hybrids. This represents the most comprehensive study of genomic prediction of hybrid performance conducted thus far

and demonstrated that hybrid performance can be predicted from genomic data with high accuracy.

### The principal role of Ku in telomere length maintenance is promotion of Est1 association with telomeres, pp. 1123–1136

Jaime M. Williams, Faissal Ouenzar, Laramie D. Lemon, Pascal Chartrand, and Alison A. Bertuch

The yeast Ku heterodimer binds DNA ends and positively regulates telomere length. Ku also associates with the RNA subunit of telomerase, TLC1. DNA and RNA binding by Ku are mutually exclusive; however, both activities are important for telomere maintenance and the mechanism by which Ku influences telomere length remains unclear. Unexpectedly, the authors find that the major role of Ku in telomere length maintenance does not lie in its previously identified functions in TLC1 nuclear localization and recruitment of the telomerase catalytic subunit. Instead, Ku interacts with the telomerase accessory subunit Est1 to promote telomere elongation.

### Testing models of the APC tumor suppressor/ $\beta$ -catenin interaction reshapes our view of the destruction complex in Wnt signaling, pp. 1285–1302

Robert J. Yamulla, Eric G. Kane, Alexandra E. Moody, Kristin A. Politi, Nicole E. Lock, Andrew V. A. Foley, and David M. Roberts

Adenomatous Polyposis Coli (APC) is a negative regulator of Wnt signaling inactivated in over 80% of colorectal cancers. APC participates in the  $\beta$ -catenin destruction complex; however, its mechanistic role remains unknown. Many models of APC function emphasize phosphorylation of its  $\beta$ -catenin binding sites. To test this hypothesis, the authors generated *Drosophila* APC2 mutants lacking  $\beta$ -catenin binding-sites. Their findings are inconsistent with current models and instead suggest that  $\beta$ -catenin binding sites increase the efficiency of  $\beta$ -catenin destruction, but do not provide a critical mechanistic function *per se*.

## This Month's Perspective

### Finding and mapping new genes faster than ever: revisited, pp. 1063–1067

James M. Sikela

This article provides a historical and personal perspective on the Human Genome Project that revisits how cDNA-based approaches were used for the initial identification and mapping of most human genes. As well as covering the scientific challenges, the article describes the excitement, uncertainty and controversy that filled the atmosphere at the time. The inclusion of a cDNA-based component, while controversial, became crucial when strategies were developed that used EST sequences to rapidly identify and map genes. These approaches led to the first partial sequences for the great majority of human genes and the first comprehensive human gene maps.

## This Month in the American Journal of Human Genetics

### The *Alu*-rich genomic architecture of *SPAST* predisposes to diverse and functionally distinct disease-associated CNV alleles

Philip M. Boone, Bo Yuan, Ian M. Campbell, Jennifer C. Scull, Marjorie A. Withers, Brett C. Baggett, Christine R. Beck, Christine J. Shaw, Pawel Stankiewicz, Paolo Moretti, Wendy E. Goodwin, Nichole Hein, John K. Fink, Moon-Woo Seong, Soo Hyun Seo, Sung Sup Park, Izabela D. Karbassi, Sat Dev Batish, Andrés Ordóñez-Ugalde, Beatriz Quintáns, María-Jesús Sobrido, Susanne Stemmler and James R. Lupski

Although copy-number variants (CNVs) are known to contribute to a range of Mendelian and complex disorders, our understanding of their molecular origins and consequences remains incomplete. Previous reports have implicated *Alu* elements in driving recombination-mediated CNV formation at several loci, including *SPAST*. Now, Boone *et al.* map the breakpoint junctions of over fifty *SPAST* CNVs at nucleotide resolution, providing evidence that the genomic architecture of this locus predisposes to a variety of CNV alleles, including several that generate chimeric transcripts. A better understanding of the phenotypic consequences brought about by the range of CNVs generated at this locus should prove helpful in both the diagnosis and treatment of spastic paraplegia.