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**Ethanol stimulates locomotion via a $G_{\alpha s}$-signalling pathway in IL2 neurons in *Caenorhabditis elegans*, pp. 1023–1039**

*James R. Johnson, Mark R. Edwards, Huw Davies, Daniel Newman, Whitney Holden, Rosalind E. Jenkins, Robert D. Burgoyne, Robert J. Lucas, and Jeff W. Barclay*

Alcohol abuse is among the top causes of preventable death, generating considerable financial, health, and societal burdens. Paradoxically, alcohol affects the brain as both a depressant and as a stimulant. Here, Johnson *et al*. demonstrate that the stimulatory effects of ethanol in *C. elegans* occur through activation of a $G_{\alpha s}$ cell signaling pathway, specifically in the chemosensory IL2 neurons of nematodes.

**Reciprocal genetics: identifying QTL for general and specific combining abilities in hybrids between multiparental populations from two maize (*Zea mays* L.) heterotic groups, pp. 1167–1180**

*Héloïse Giraud, Cyril Bauland, Matthieu Falque, Delphine Madur, Valérie Combes, Philippe Jamin, Cécile Monteil, Jacques Laborde, Carine Palaffre, Antoine Gaillard, Philippe Blanchard, Alain Charcosset, and Laurence Moreau*

Understanding genetic architecture of hybrid performances is important for species showing heterosis. Giraud *et al.* evaluated an original mating design between two multiparental populations representing two maize heterotic groups. Using a linkage analysis model, they detect QTLs affecting General Combining ability (GCA) and some loci with mild effects on Specific Combining Ability (SCA). Relative to tester-based designs, use of hybrids between two multiparental populations appears highly cost efficient to detect simultaneously QTL in two heterotic groups.

**Extended synaptotagmin localizes to presynaptic ER and promotes neurotransmission and synaptic growth in *Drosophila*, pp. 993–1006**

*Koto Kikuma, Xiling Li, Daniel Kim, David Sutter, and Dion Dickman*

In highly polarized neurons, an extensive endoplasmic reticulum (ER) network extends to distal dendrites and axons. Several human diseases result from defective neuronal ER, but this network remains poorly understood at synapses. Using the *Drosophila* neuromuscular junction, Kikuma *et al*. find a $Ca^{2+}$ sensing protein, Extended Synaptotagmin (Esyt), is localized to presynaptic ER and promotes synaptic transmission and growth. Esyt couples synaptic activity to presynaptic ER responses, highlighting the first in vivo function of this conserved gene family.

**Will big data close the missing heritability gap?, pp. 1135–1145**

*Hwasoon Kim, Alexander Grueneberg, Ana I. Vazquez, Stephen Hsu, and Gustavo de los Campos*

Modern biobanks that collect genotype-phenotype information from hundreds of thousands of individuals bring unprecedented opportunities for genomic research. Here, Kim *et al*. use the UK Biobank data to assess whether Big Data can substantially reduce the Missing Heritability gap. Using human height as a model trait, they show that prediction R-squared increases monotonically with sample sizes, achieving a prediction R-squared of 24% with a training size of n=80,000. Using data-partitions, they profile prediction R-squared versus sample sizes and forecast that prediction R-squared will be considerably higher as larger data sets become available.

**Rapid DNA synthesis during early *Drosophila* embryogenesis is sensitive to maternal humpty dumpty protein function, pp. 935–947**

*Shera Lesly, Jennifer L. Bandura, and Brian R. Calvi*

Lesly, Bandura, and Calvi show that rapid DNA synthesis during early *Drosophila* embryogenesis is highly sensitive to mild mutations in the maternally-encoded Humpty dumpty protein, providing further insight into the enigmatic S/M cycles that begin *Drosophila* development. This study defines two timepoints during *Drosophila* development that are particularly sensitive to hypomorphic mutations in essential DNA replication protein genes, with important implications for how mutations in these genes cause tissue-specific effects in human microcephalic dwarfism syndromes.

**Mitigating mitochondrial genome erosion without recombination, pp. 1079–1088**

*Arunas L. Radzvilavicius, Hanna Kokko, and Joshua R. Christie*

A long-standing unresolved question is how uniparentally inherited mitochondria evade Muller's ratchet. Radzvilavicius, Kokko, and Christie find that, in the absence of recombination, uniparental inheritance of freely-segregating mitochondrial genomes is sufficient to maintain negligible rates of Muller's ratchet. Critically, paternal leakage always results in higher equilibrium mutation load, even when high rates of recombination eliminate Muller's ratchet. They explore the effects of mitochondrial bottlenecks and fusion-fission cycles, finding that they both act as mechanisms of mitochondrial quality control.

**COMBAT: a combined association test for genes using summary statistics, pp. 883–891**

*Minghui Wang, Jianfei Huang, Yiyuan Liu, Li Ma, James B. Potash, and Shizhong Han*

Many gene-based association tests have been proposed for genome-wide association studies (GWAS). However, the power of existing gene-based tests is often dependent on the underlying genetic models, and it is not known *a priori* which test is optimal. Wang *et al*. propose a combined association test (COMBAT) for genes, which incorporates strengths from existing gene-based tests and shows higher overall performance than any individual test. Through reanalysis of the meta-analytic results of GWAS for bipolar disorder, COMBAT not only detected well-established bipolar risk genes, it also identified novel genes that reached genome-wide significance in larger samples.

**Body shape and coloration of silkworm larvae are influenced by a novel cuticular protein, pp. 1053–1066**

*Gao Xiong, Xiaoling Tong, Tingting Gai, Chunlin Li, Liang Qiao, Antónia Monteiro, Hai Hu, Minjin Han, Xin Ding, Songyuan Wu, Zhonghuai Xiang, Cheng Lu, and Fangyin Dai*

Body shape and color patterns of insect larvae are fundamental traits for survival. Typically, transcription factors or members of signaling pathways are thought to control these two traits during development. Xiong *et al*. report that a novel cuticular protein affects body shape and coloration simultaneously, suggesting that the gene has undergone neofunctionalization after duplication. This is the first study to identify a molecule whose pleiotropic function affects the development of both body shape and color patterns in insect larvae.

## This Month in the American Journal of Human Genetics

**Inferring relevant cell types for complex traits using single-cell gene expression, Am. J. Hum. Gent. 101**

*Diego Calderon, Anand Bhaskar, David A. Knowles, David Golan, Towfique Raj, Audrey Q. Fu, and Jonathan K. Pritchard*

To achieve meaningful biological insights into complex traits requires that begin to investigate traits of interest in relevant cell types. The development of technologies able to measure gene expression at the level of single cells provides an opportunity to explore complex trait genetics at a resolution not previously achievable. To date, however, there has not been a systematic way to match phenotypes of interest to data collected from single-cell gene expression studies. To address this deficiency, Calderon *et al*. develop RolyPoly, a model that integrates GWAS summary statistics and gene expression data to identify cell types of interest. Armed with such knowledge, investigators should be better positioned to pinpoint causative variants and move from SNPs to function.