Ethanol stimulates locomotion via a Gα- signalling pathway in IL2 neurons in Caenorhabditis elegans, pp. 1023–1039
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 Gαs 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
Hélène Giraud, Cyril Bauland, Matthieu Falague, 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 Ca2+ sensing protein, Extended Synaptotagmin (Esyn), 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 Gruenenberg, Ana I. Vasques, 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, Yiyan 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, Minjun Han, Xin Ding, Songyuan Wu, Zhonghui Xiang, Cheng Lu, and Fangxin 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. Genet. 101
Diego Calderon, Anand Bhaskar, David A. Knowles, David Golan, Towfiq 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. developed 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.