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**Mutational pleiotropy and the strength of stabilizing selection within and between functional modules of gene expression, pp. 1601–1616**

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

Collet *et al*. adopt a high-dimensional quantitative genetic approach using gene expression traits to test for the presence of modularity of the genotype-phenotype map, where traits contributing to the same function (functional modularity) are more strongly genetically correlated (variational modularity) than traits belonging to different functions. They find little evidence that functional modules predict variational modules when investigating functional module specific levels of (i) mutational pleiotropy, (ii) standing genetic covariance, and (iii) stabilizing selection against mutational pleiotropy. However, they detect large variational modules spanning several functional modules.

**A damage sensor associated with the cuticle coordinates three core environmental stress responses in *Caenorhabditis elegans*, pp. 1467–1482**

*William Dodd, Lanlan Tang, Jean-Christophe Lone, Keon Wimberly, Cheng-Wei Wu, Claudia Consalvo, Joni E. Wright, Nathalie Pujol, and Keith Choe*

Although extracellular matrices function as protective barriers to many types of environmental insult, their role in sensing stress and regulating adaptive gene induction responses has not been studied carefully. Here, Dodd *et al*. identify a specific structural feature in the collagenous extracellular cuticle of the nematode *C. elegans* as a regulator of conserved transcription responses to oxidative, osmotic, and pathogenic stressors. They also explore downstream transcription factor requirements. Their results are consistent with the presence of an extracellular sensor for damage that regulates three distinct stress-inducible responses in the nuclei of epidermal cells.

**Beyond thermodynamic constraints: evolutionary sampling generates realistic protein sequence variation, pp. 1387–1395**

*Qian Jiang, Ashley I. Teufel, Eleisha L. Jackson, and Claus O. Wilke*

The computational design of protein sequences has yielded major successes in several application areas. However, when the principles of protein design are applied to molecular evolution, results tend to be poor. In particular, alignments of designed protein sequences deviate in important and quantifiable ways from natural sequence alignments. Jiang and Teufel *et al*. show that by coupling protein design with a realistic model of sequence evolution, the discrepancies between simulated and natural sequence alignments can be resolved. The work highlights how important evolutionary sampling of sequence space is for the computational generation of realistic sequence alignments.

**Plasticity of meiotic recombination rates in response to temperature in *Arabidopsis*, pp. 1409–1420**

*Andrew Lloyd, Chris Morgan, F. Chris H. Franklin, and Kirsten Bomblies*

Meiosis, the specialized cell division that generates gametes, shuffles parental genomes through homologous recombination. It was reported in *Drosophila* a century ago, that the recombination rate is sensitive to temperature, but how or why has remained largely mysterious. Understanding the plasticity of recombination in response to environmental factors such as temperature, has important implications for inheritance, evolution, and breeding, and for interpreting the causes of recombination rate variation in nature. Here, Lloyd *et al*. show that, in *Drosophila*, both high and low temperatures increase meiotic recombination rates in the plant *Arabidopsis thaliana* and provide novel mechanistic insights into this phenomenon.

**Mito-nuclear interactions affecting lifespan and neurodegeneration in a *Drosophila* model of Leigh syndrome, pp. 1535–1552**

*Carin A. Loewen and Barry Ganetzky*

Mitochondrial function requires coordinated activities of interacting proteins encoded in both the nuclear and mitochondrial genomes. Nuclear mutations cause human mitochondrial disorders that commonly exhibit unexplained clinical variability (e.g. age of onset and severity). Genetic variation in mitochondrial genomes has been suggested to cause phenotypic modification of nuclear-encoded mitochondrial mutations but direct evidence is scarce. Loewen and Ganetzky characterized a nuclear-encoded mitochondrial mutant in *Drosophila* and showed that variation in phenotypic severity is associated with otherwise silent mitochondrial sequence variants. This work demonstrates that mito-nuclear interactions can impact mitochondrial disease and provides a powerful experimental system to further investigate mito-nuclear interactions.

**A perfect match genomic landscape provides a unified framework for the precise detection of variation in natural and synthetic haploid genomes, pp. 1631–1641**

*Kim Palacios-Flores, Jair García-Sotelo, Alejandra Castillo, Carina Uribe, Luis Aguilar, Lucía Morales, Laura Gómez-Romero, José Reyes, Alejandro Garciarubio, Margareta Boege, and Guillermo Dávila*

At the heart of genomics lies the precise determination of an organism's DNA sequence. Palacios-Flores *et al*. present a simple, sensitive, precise, and essentially non-statistical solution for generating genome-wide variation profiles and refining reference genomes with single nucleotide resolution. Analyses of natural genomes and a synthetic *S. cerevisiae* chromosome demonstrate the power of this strategy by uncovering previously unidentified variants. The authors also propose a theoretical framework for defining a general signature of genome variation.

**Seven-up is a novel regulator of insulin signaling, pp. 1643–1656**

*Laura Palanker Musselman, Jill L. Fink, Ezekiel J. Maier, Jared A. Gatto, Michael R. Brent, and Thomas J. Baranski*

Musselman *et al*. address the overarching question: "What's so bad about a high-calorie diet?" Using computational biology to analyze mRNA expression profiles, the authors built a *Drosophila* fat body gene regulatory network that predicted a role for the transcription factor Seven-up (Svp) in promoting health in the face of a high-calorie diet. Svp promotes insulin signaling, glucose uptake, and lipid homeostasis. Other genes in the regulatory network could also be new modifiers of diet-induced obesity.

**Detecting polygenic adaptation in admixture graphs, pp. 1565–1584**

*Fernando Racimo, Jeremy J. Berg, and Joseph K. Pickrell*

Polygenic adaptation occurs when natural selection changes the average value of a complex trait in a population, via small shifts in allele frequencies at many loci. Here, Racimo, Berg, and Pickrell present a method to detect polygenic adaptation using an admixture graph, which describes the splits and admixture events relating different populations through time. They provide evidence that variants associated with traits like height, educational attainment, and self-reported unibrow have been influenced by polygenic adaptation in humans. They expect their method will allow researchers to understand how complex traits evolved, using an interpretable framework that harnesses theory from both quantitative and population genetics. See the accompanying commentary by John Novembre and Nicholas H. Barton in this issue.