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Evolutionary loss of genomic proximity to conserved noncoding elements impacted the gene expression dynamics during mammalian brain development, pp. 1239–1254

Meenakshi Bagadia, Keerthivasan Raanin Chandradoss, Yachna Jain, Harpreet Singh, Mohan Lal, and Kuljeet Singh Sandhu

Loss of linear proximity between a gene and its regulatory element can alter its expression. Bagadia and Chandradoss *et al*. report a significant loss of proximity between evolutionarily constrained non-coding elements and adjacent brain development genes in rat. The separation of genes and their regulatory elements was strongly associated with the evolutionary loss of developmental gene expression pattern in the rat brain and coincided with the loss of brain traits. This study highlights the importance of the relative chromosomal positioning of genes and their regulatory elements in the evolution of phenotypes.

Adjusting for principal components of molecular phenotypes induces replicating false positives, pp. 1179–1189

Andy Dahl, Vincent Guillemot, Joel Mefford, Hugues Aschard, and Noah Zaitlen

Biological, technical, and environmental confounders are ubiquitous in the high-dimensional, high-throughput functional genomic measurements being used to understand cellular biology and disease processes, and many approaches have been developed to estimate and correct for unmeasured confounders. Here, Dahl *et al*. explore the specific assumptions made by these models and show that correction approaches induce replicating false positives in several realistic simulations, proving it theoretically for principal component analysis. They demonstrate an under-appreciated source of replicating false positives in functional genomic studies and recommend best practices.

Dissection of complex, fitness-related traits in multiple *Drosophila* mapping populations offers insight into the genetic control of stress resistance, pp. 1449–1467

Elizabeth R. Everman, Casey L. McNeil, Jennifer L. Hackett, Clint L. Bain, and Stuart J. Macdonald

The ability to survive periods without food is an important component of individual fitness, and genetic dissection can provide insight into the mechanisms and evolution of starvation resistance. Everman *et al*. use several genome-wide screens to identify numerous genetic positions that impact starvation in flies and find largely non-overlapping sets of significant sites in each case. They further show that, while a variant significant in one dataset was rarely significant in the others, the sign of the effect was typically preserved, implying that starvation susceptibility is influenced by an array of small-effect variants that commonly do not survive rigorous genome-wide statistical testing.

Integration of self and non-self recognition modulates asexual cell-to-cell communication in *Neurospora crassa*, pp. 1255–1267

Monika S. Fischer, Wilfried Jonkers, and N. Louise Glass

Cells cooperate, compete, and are attacked in nature, driving the evolution of mechanisms for recognizing self versus non-self. Filamentous fungal cells cooperate to form an interconnected colony while competing with genetically dissimilar colonies for resources. Here, Fischer, Jonkers, and Glass use reporter constructs to define networks that regulate somatic cell fusion in the filamentous fungus *Neurospora crassa*. Their data support a model of integrated self and non-self recognition processes that modulate somatic cell-to-cell communication and cooperation between identical and non-identical cell types.

A shift in aggregation avoidance strategy marks a long-term direction to protein evolution, pp. 1345–1355

Scott G. Foy, Benjamin A. Wilson, Jason Bertram, Matthew H. J. Cordes, and Joanna Masel

The current consensus among biologists is that evolution does not have a direction. Here, Foy *et al*. compare recently-born gene families to genes that are chronologically "more evolved," finding a striking directionality in the evolution of the structural properties of proteins, which must balance the need to fold in a functional manner against the need to avoid misfolding. Young genes use a primitive strategy to avoid protein misfolding, while old genes use a much more subtle strategy, suggesting a progressive shift in protein folding strategy over billions of years.

Layers of cryptic genetic variation underlie a yeast complex trait, pp. 1469–1482

Jonathan T. Lee, Alessandro L. V. Coradini, Amy Shen, and Ian M. Ehrenreich

To better understand cryptic genetic variation, Lee *et al*. comprehensively map the genetic basis of a trait that is typically suppressed in a yeast cross. By determining how three different genetic perturbations give rise to the trait, they identify 21 loci harboring cryptic genetic variants, nearly all of which play roles in the transcriptional regulation of the same key gene. By examining these loci in greater detail, they show that the perturbations affect every aspect of the trait's genetic architecture, including which cryptic genetic variants have phenotypic effects, as well as the extent of additivity, epistasis, and genotype-environment interaction among these variants.

Necessity and contingency in developmental genetic screens: EGF, Wnt, and semaphorin pathways in vulval induction of the nematode *Oscheius tipulae*, pp. 1315–1330

Amhed M. Vargas-Velazquez, Fabrice Besnard, and Marie-Anne Félix

Genetic screens in the nematode *Caenorhabditis elegans* have identified EGF and Notch pathways as key for vulval precursor cell fate patterning. Here, Vargas-Velazquez, Besnard, and Félix report on the molecular identification of mutations affecting vulval induction in another nematode, *Oscheius tipulae*. They find that mutations resulting in an excess of secondary fates unexpectedly correspond to the plexin/2semaphorin pathway, which is not implicated in vulval induction in *C. elegans*, highlighting both necessity and contingency in forward genetic screens.

Complex trait prediction from genome data: contrasting EBV in livestock to PRS in humans, pp. 1131–1141

Naomi R. Wray, Kathryn E. Kemper, Benjamin J. Hayes, Michael E. Goddard, and Peter M. Visscher

Genomic estimated breeding values (GEBVs) in livestock and polygenic risk scores (PRS) in humans are conceptually similar; however, the between-species differences in linkage disequilibrium (LD) provide a fundamental point of distinction that impacts approaches to data analyses. The differences in LD are driven by differences in effective population size, which in turn reflects differences in family size. Wray *et al*. review concepts that have different priorities between species and use this background to address frequently asked questions.

This Month's Perspectives

From R.A. Fisher's 1918 paper to GWAS a century later

Peter M. Visscher and Michael E. Goddard

The genetics and evolution of complex traits, including quantitative traits and disease, have been hotly debated ever since Darwin. A century ago, a paper from R.A. Fisher reconciled Mendelian and biometrical genetics in a landmark contribution that is now accepted as the foundation stone of the field of quantitative genetics. Here, Visscher and Goddard give their perspective on the Fisher 1918 paper in the context of how and why it is relevant in today's genome era. The authors mostly focus on human trait variation, in part because Fisher did so too, but the conclusions are general and extend to other natural populations and to populations undergoing artificial selection.