Evolving mistranslating tRNAs through a phenotypically ambivalent intermediate in Saccharomyces cerevisiae, pp. 1865–1879
Matthew D. Berg, Kyle S. Hoffman, Julie Geneveux, Safie Mian, Ryan S. Trauster, David B. Hamford, Patrick O'Donnogue, and Christopher J. Brandl

It is increasingly apparent that the genetic code is not static and that organisms use variations in the genetic code for selective advantage. Berg et al. investigate the mechanisms by which mistranslating tRNAs occur and how the genetic code evolves by examining the selection of serine tRNAs that incorrectly add serine at proline codons in Saccharomyces cerevisiae. They show that a serine tRNA with a proline anticodon is toxic; however, mistranslating tRNAs can evolve through intermediate tRNA variants that decrease function. tRNAs with these “ambivalent” mutations are maintained in cells, with no obvious consequence. If the ambivalent intermediates undergo an anticodon mutation, mistranslation results at low, non-toxic levels.

Towards universal forward genetics: using a draft genome sequence of the nematode Oscheius tipulae to identify mutations affecting vulva development, pp. 1747–1761
Fabrice Besnard, Georgios Koutsovoulos, Sara Deudonné, Mark Blaxter, and Marie-Anne Felix

Understanding evolution requires the comparison of more than a few model species, and exploration of the genotype/phenotype relationship is limited for species without fully sequenced genomes. Besnard and Koutsovoulos et al. propose a rapid, cost-effective procedure that iteratively uses a draft genome assembly and genetic mapping by-sequencing to perform forward genetics. Using the nematode Oscheius tipulae, they identified the phenotyping-causing mutations in vulva mutants of the cod-3 gene, revealing unexpected orthology with C. elegans mig-15. Their method provides a roadmap for forward genetics in non-model species.

Canalization by selection of de Novo induced mutations, pp. 1995–2006
Laura Fanti, Lucia Piacentini, Ugo Cappucci, Assunta M. Casale, and Sergio Pimpinelli

Waddington elaborated the concepts of “canalization and assimilation” to explain how an apparently somatic, stress-induced variant could become heritable through the germline in Drosophila. He resolved this seemingly Lamarckian phenomenon by positing the existence of cryptic mutations that can be expressed and selected under stress. To investigate the relevance of such mechanisms, Fanti and Piacentini et al. performed experiments similar to Waddington’s before isolating and fixing phenotypic variants. Their analysis of these variants revealed they were generated de novo by transposon insertions or DNA deletions, thus highlighting a novel mechanism for the apparent assimilation process of an acquired character.

Networks underpinning symbiosis revealed through cross-species eQTL mapping, pp. 2175–2184

Interactions between species are pervasive among plants, animals, and microbes, and identifying the molecular signals involved is an active area of research. Since existing analysis tools often focus on only one of the species involved in an interaction, Guo et al. developed an approach that identifies genes concurrently in both interacting partners. By applying this methodology to plants infected with a parasitic nematode, they constructed cross-species gene networks. In these, genetic variants producing molecular signals were connected to both the plant and parasite genes reacting to those signals.

Shrinking daughters: Rlm1-dependent G1/S checkpoint maintains Saccharomyces cerevisiae daughter cell size and viability, pp. 1923–1938
Sarah Piccirillo, Deepshikha Neog, David Spade, J. David Van Horn, Lauren M. Tiede-Lewis, Sarah L. Dallas, Tamas Kapros, and Saul M. Honigberg

How do cells ensure everything is set for cell division before they start the process? Piccirillo et al. demonstrate that a checkpoint in budding yeast can delay the birth of new buds in response to cell-wall stress. In an rlm1Δ mutant, this checkpoint was bypassed, resulting in precocious bud emergence. These precocious buds grew into daughter cells, but after cytokinesis the daughter cells suddenly shrank and died. In contrast, mother cells continued to divide, resulting in a characteristic “satellite group” morphology. By restoring the G1 delay to the mutant, Piccirillo et al. restored normal daughters and so conclude that the checkpoint monitors an event in G1 that is needed after cytokinesis.

A lysine desert protects a novel domain in the Sxl5-Sxl8 SUMO targeted Ub ligase To maintain sumoylation levels in Saccharomyces cerevisiae, pp. 1807–1821
Pragati Sharma, Janet R. Mullen, Minxing Li, Mikel Zarategui, Samuel F. Bunting, and Steven J. Brill

Sumoylation is required to repair protein-linked DNA damage, but its presence can limit the use of alternative repair pathways. Through a suppressor screen of mutants sensitive to protein-linked DNA damage, Sharma et al. isolated a variety of SUMO regulators, including two alleles of the ubiquitin ligase subunit Sxl5-K. These alleles created new lysine residues, highlighting the presence of a 400 amino acid lysine desert normally found within the Sxl5 ligase. The new lysines resulted in auto-ubiquitination, partial Sxl5 degradation, and increased global polysumoylation. The lysine desert is one solution to the problem that ubiquitin ligases face when evolving new domains.

Rapid evolution of ovarian-biased genes in the yellow fever mosquito (Aedes aegypti), pp. 2191–2137
Carrie A. Whittle and Cassandra G. Etovar

Males and females exhibit marked differences in phenotypes and gene expression, particularly in the gonads. Genes with male- or testis-biased expression typically have been shown to evolve rapidly in metazoans. Here, Whittle and Etovar provide an uncommon example that shows rapid evolution of protein sequences and shifts in codon usage of ovary-biased genes in the mosquito Aedes aegypti. They propose that this fast evolution may be explained by sexual selection during male swarming, ovary-sperm chemotaxis, and/or reduced male-male sperm competition.

Powerful genetic association analysis for common or rare variants with high-dimensional structured traits, pp. 1779–1790
Xiang Zhan, Ni Zhao, Anna Plantinga, Timothy A. Thornton, Karen N. Conney, Michael E Epstein, and Michael C. Wu

Genetic association studies often collect a wide range of complex traits, including high-dimensional and structured omics measurements. The complex nature of these data poses a challenge for traditional statistical and computational methods. Zhan et al. propose a novel method for testing the association between these high-dimensional structured traits and a set of common or rare genetic variants. By incorporating the high-dimensionality and structure in traits, their approach provides a new method that is methodologically flexible, biologically meaningful, statistically powerful, and computationally efficient.

This Month in the American Journal of Human Genetics

CRISPR/Cas9 mediated scanning for regulatory elements required for HPRT1 expression via thousands of large, programmed genomic deletions Am. J. Hum. Genet. 101(2)
Molly Gasperini, Gregory M. Findlay, Aaron McKenna, Jennifer H. Milbank, Choli Lee, Melissa D. Zhang, Darren A. Cusanovich, and Jay Shendure

The majority of known mutations that underlie Mendelian disorders lie in the coding region; the contribution of noncoding regions remains unclear. Now, Gasperini et al. devised a CRISPR/Cas9-based screening system, which they term ScanDel, to address the contribution of noncoding sites to phenotypes relevant to human disease. In a ScanDel screen, thousands of programmed deletions are used to scan a region of interest in a cell-based assay. Proof-of-concept work at the HPRT1 locus suggests that variation in distal regions most likely does not contribute substantially to Lesch-Nyhan syndrome mutational burden. Further application of ScanDel will enable high-throughput interrogation of the contribution of noncoding genome to human disease.