IN BRIEF

GENETICS

Disease heritability explained by eQTLs

Yao, D. W. et al. *Nat. Genet.* **52**, 626–633 (2020).

Genome-wide association studies (GWAS) and expression quantitative trait locus (eQTL) analyses can identify genetic variants associated with complex traits and gene expression, respectively. Previous studies showed overlap between these two types of signal, suggesting a potential impact of gene expression levels on phenotypic variability. Although several strategies exist for quantifying this effect, distinguishing directionally mediated effects from alternatives such as pleiotropy and linkage is difficult. Yao et al. define heritability mediated by the *cis* genetic component of gene expression levels and develop a statistical method called mediated expression score regression (MESC) for estimation using GWAS and *cis*-eQTL summary statistics. MESC does not depend on significance thresholds to filter genes or SNPs and achieves unbiased estimates with well-calibrated standard errors. The researchers analyzed data from 42 traits and 48 tissues, and found only about 11% of heritability was mediated by assayed gene expression levels. *LT**

https://doi.org/10.1038/s41592-020-0897-6

NEUROSCIENCE

The mouse reference brain in 3D

Wang, Q. et al. *Cell* **181**, 936–953 (2020).

Many image datasets of the mouse brain require registration to a reference atlas; for example, for annotation or comparison between datasets. The Allen Mouse Brain Common Coordinate Framework serves this purpose and is now presented in its third version (CCFv3). CCFv3 is based on 1,675 mouse brains, which were stained with various histological techniques, and has an isotropic resolution of 10 micrometers, thereby surpassing existing reference brain atlases. In contrast to previous atlases, CCFv3 is parcellated in 3D, which avoids irregular borders between its 658 annotated structures. Furthermore, the parcellation is based on multiple image modalities, ensuring unprecedented accuracy. The reference brain atlas and its underlying datasets can be viewed in the dedicated interactive Atlas Viewer, while the data are also available for download. CCFv3 can be accessed at https://atlas.brain-map.org/. *NV*

https://doi.org/10.1038/s41592-020-0899-4

MICROSCOPY

Expanding worms

Yu, C.-C. et al. *Elife* **9**, e46249 (2020).

Expansion microscopy (ExM) is a method whereby samples are physically expanded using embedded, swellable hydrogels. Upon imaging using standard microscopes, the image resolution achieved is improved by the degree of change in sample size, meaning, for example, that a fourfold linear expansion improves resolution fourfold, yielding super-resolution images. ExM has been used extensively on tissues and cells. Now Yu et al. have developed a workflow to apply ExM to *Caenorhabditis elegans*. The method, called ExCel, modifies previous protocols and incorporates steps that deal with the worm's cuticle, which is too stiff to allow expansion and is impenetrable to many small molecules. The researchers show they can expand intact worms and achieve ~70-nm resolution using a protocol with ~4.5-fold linear expansion. They further show they can image proteins, RNA and DNA, and present protocols that are compatible with fluorescent protein imaging and endogenous epitope imaging. They also describe iterative ExCel, which allows 20-fold linear expansion. *RS*

https://doi.org/10.1038/s41592-020-0898-5

MOLECULAR BIOLOGY

Design of improved pET expression plasmids

Shilling, P. J. et al. *Commun. Biol.* **3**, 214 (2020).

The pET expression plasmids are among the most popular plasmids for high levels of recombinant protein expression in *Escherichia coli*. These were originally designed more than 30 years ago, and even though the original design has been expanded to 103 unique plasmids, the transcription and translation control elements have remained the same. Shilling et al. have revisited the design of the pET28a plasmid, the most popular of the series. They first added the full T7 promoter sequence, which had originally been truncated upon insertion of the lac operator. Restoring the full T7 consensus sequence conferred a threefold increase in protein production. Next, they synthetically evolved the translation initiation region (TIR) which had originally formed by ad hoc genetic fusion. By screening for optimal ribosome binding, they were able to increase protein production up to 47-fold. In combination, these two strategic changes give a 33- to 121-fold increase. This approach is easy to incorporate and can be used with the other pET expression plasmids as well. *AS*

https://doi.org/10.1038/s41592-020-0904-y