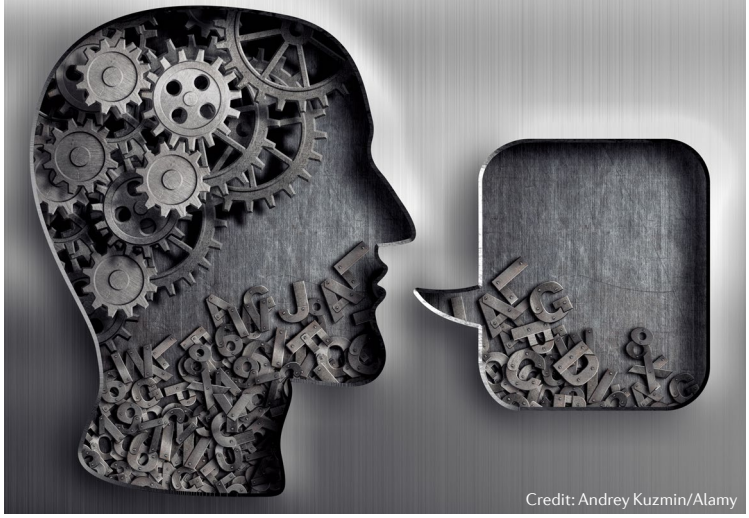

Credit: Andrey Kuzmin/Alamy

population sampling and insufficient consideration of the differing patterns of genetic variation across populations due to demography.

The team then looked at genomic evolutionary rate profiles, a more sophisticated approach to analysing conservation levels across multiple species. They identified an intronic region of interest in *FOXP2* containing multiple single-nucleotide polymorphisms (SNPs) unique to humans and common among them, but these mutations are variable among different populations. The region is expressed in human brain at low levels and is potentially an enhancer, but its function is otherwise unclear.

Overall, while the argument for a function of FOXP2 in human language remains, its contribution to the evolution of this trait now seems less evident. With the advantage of better data, the impact of differences in sampling and other parameters can be shown, providing valuable lessons for other studies.

Rebecca Furlong, Senior Editor,
Nature Communications

ORIGINAL ARTICLE Atkinson, A. G. et al. No evidence for recent selection at *FOXP2* among diverse human populations. *Cell* **174**, 1–12 (2018)
FURTHER READING Enard, W. et al. Molecular evolution of *FOXP2*, a gene involved in speech and language. *Nature* **418**, 869–872 (2002)

SNP effect sizes were calculated and the median effect per allele of lead SNPs was found to correspond to 1.7 weeks of schooling.

Autosomal SNPs were annotated using DEPICT software and a striking enrichment of SNPs near genes implicated in the central nervous system, specifically with neurophysiological functions and synaptic plasticity, was observed. Of note was the absence of enrichment of glia cell and myelination gene sets. The authors point out that this might be considered an argument against the hypothesis of individual differences in cognition being driven by differences in axonal transmission speed.

To achieve polygenic prediction of education, various polygenic scores were calculated and the predictive power was found to be greater the more SNPs were included, that is, the less stringent the significance threshold for inclusion was. The best score reached a predictive accuracy of 12.7% and 10.6%, respectively, in the two tested independent cohorts — a better predictor than household income but less predictive than the educational attainment of the parents.

Despite the staggering numbers that this GWAS reports, both in terms of sample size and identified SNPs, challenges remain. The authors discuss the need for inclusion of more diverse ancestries and raise the issue of imperfect genetic correlation of the phenotype across cohorts owing to educational systems differing locally and over time, something that has to be taken into account in power calculations and study design. With a phenotype as highly dependent on the environment as educational attainment, the authors further caution that polygenic score effects may represent in part environmental influences shared with the parents.

Michelle Trenkmann, Associate Editor,
Nature Communications

ORIGINAL ARTICLE Lee, J. J. et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat. Genet.* **50**, 1112–1121 (2018)
FURTHER READING Plomin, R. & von Stumm, S. The new genetics of intelligence. *Nat. Rev. Genet.* **19**, 148–159 (2018)

TECHNOLOGY

Transcriptomics in intact tissues

Single-cell approaches such as single-cell RNA sequencing (scRNA-seq) are essential to detect biologically relevant variability between cells or define the characteristics of rare cell types. Adapted methods such as in situ RNA-seq have tackled the challenge of capturing spatial context, but have yet to be applied to whole tissues owing to limitations such as low efficiency and scalability. A newly developed technology for 3D intact-tissue RNA-seq, named STARmap (spatially-resolved transcript amplicon readout mapping), promises to yield gene expression profiles while retaining 3D positional information at cellular resolution.

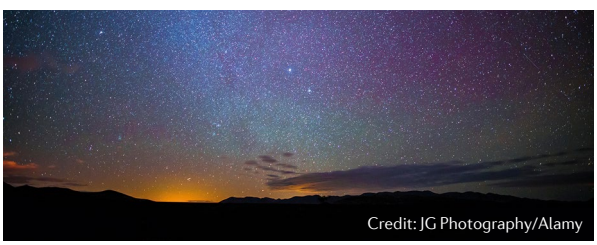
Recently developed in situ hybridization methods enable high-resolution imaging of RNAs within intact tissues by exploiting hydrogel-tissue chemistry (HTC) to link in situ-synthesized polymers with RNAs. Wang et al. hypothesized that exploiting HTC to convert a tissue into a hydrogel-embedded form might enable the application of in situ RNA-seq to the hydrogel-tissue formulation.

In STARmap, to start, all cellular RNAs are labelled with two probes, one of which contains a five-base barcode, providing a gene-unique identifier for later multiplexed gene detection. To reduce noise, both probes must hybridize to the same RNA molecule for enzymatic amplification to occur, which generates a DNA nanoball (amplicon) that contains multiple copies of the cDNA probes. DNA amplicons are then anchored to an in situ-synthesized polymer network before removing proteins and lipids. This process transforms the tissue into a 3D hydrogel–DNA chip that can be used for sequencing. The identities of RNA transcripts, represented by DNA amplicons, are identified and quantified on the basis of the five-base barcode using a sequencing-by-ligation method with two-base encoding for error reduction, termed SEDAL (sequencing with error-reduction by dynamic annealing and ligation). SEDAL decodes DNA sequences into multi-coloured fluorescence signals that can be imaged. The authors validate their method by efficiently and reproducibly mapping 160 to 1,020 genes simultaneously in sections of mouse brain at single-cell resolution.

By combining HTC, targeted signal amplification and in situ sequencing, STARmap enables not only the quantification of gene expression in single cells but also the identification and mapping of cell types in 3D.

Linda Koch

ORIGINAL ARTICLE Wang, X. et al. Three-dimensional intact-tissue sequencing of single-cell transcriptional states. *Science* **361**, eaat5691 (2018)
FURTHER READING Crosetto, N. et al. Spatially resolved transcriptomics and beyond. *Nat. Rev. Genet.* **16**, 57–66 (2015)


Credit: JG Photography/Alamy