Correlation analyses for loneliness revealed genetic overlap with 36 complex traits, including strong positive correlations with depressive symptoms and body mass index (BMI). Excluding individuals with self-reported depression from a repeat loneliness GWAS did not alter the original outcome, indicating that the 15 loci do not affect loneliness as a consequence of depressive tendencies. By contrast, bi-directional Mendelian randomization analyses suggested a causal effect of BMI on loneliness — but not of loneliness on BMI — and a positive bidirectional causal relationship between depressive symptoms and BMI.

Future studies should investigate the link between cardiometabolic health and social well-being and aim to identify modifiable risk factors that could reduce social isolation in susceptible individuals.

Dorothy Clyde

ORIGINAL ARTICLE Day, F. R. et al. Elucidating the genetic basis of social interaction and isolation. *Nat. Commun.* **9**, 2457 (2018)

metabotropic glutamate receptor 5 (mGluR5) as a target, which shows aberrant activation in the *Fmr1* knockout mouse, a model of human FXS. mGluR5–CRISPR-Gold injected stereotaxically into the striatum of mice not only reduced mGluR5 protein levels in the affected areas but also led to alleviation of the repetitive behaviours in *Fmr1* knockout mice without significant changes in general locomotor activity.

While CRISPR-Gold does not achieve cell type-specific delivery of gene-editing ribonucleoproteins and only acts within a restricted area around the injection site, it offers a virus-free alternative without detectable toxicities as a stepping stone towards gene-editing in the brain and the treatment of genetic neurological disorders.

Michelle Trenkmann, Associate Editor, Nature Communications

ORIGINAL ARTICLE Lee, B. et al. Nanoparticle delivery of CRISPR into the brain rescues a mouse model of fragile X syndrome from exaggerated repetitive behaviours. *Nat. Biomed. Eng.* **2**, 497–507 (2018)

Credit: Michael Siward/Moment/Getty

GENOMICS

Koala genome insights

A new study in *Nature Genetics* leverages long-read sequencing to generate a high-quality reference genome for the modern koala, *Phascolarctos cinereus*, and reports various inferences about adaptation and conservation of this species classified as 'vulnerable'.

Johnson et al. used a multi-layered strategy for genome sequencing and assembly involving 57.3-fold coverage with Pacific Biosciences (PacBio) long-read sequencing. The long reads were locally assembled into contigs and polished for quality using 30-fold coverage with Illumina short reads. The contigs were then assembled into higher-order chromosome scaffolds using a combination of optical mapping and synteny information based on knowledge of gene order along the chromosomes of other marsupials. Overall, the resultant 3.42 Gb reference genome assembly is the highest-quality marsupial genome to date.

Koalas are known for their specialized diets, consisting mainly of toxin-containing eucalyptus leaves and are thought to have acute senses of smell and taste for food selectivity. Searching for noteworthy characteristics of koala genes linked to smell and taste, the authors identified an expansion of one lineage of vomeronasal receptor type 1 (*V1R*) genes, which is consistent with an enhanced ability to detect plant secondary metabolites. By contrast, the koala had fewer regular olfactory receptor genes than other marsupials, in line with dietary specialists often having fewer olfactory receptors than species with broader diets. For taste, marsupial-specific expansions followed by koala-specific duplications in the *TAS2R* family resulted in 24 *TAS2R* genes in koalas. This is among the greatest number of taste genes found in mammals, and their function for detecting bitter-taste toxins may enable koalas to choose lower-toxicity leaves to reduce toxin consumption.

A eucalyptus leaf diet would be lethal to most mammals, so the team investigated the potential genetic basis of the enhanced detoxification ability of koalas. The authors identified a lineage-specific expansion in the cytochrome P450 monooxygenase 2C (*CYP2C*) family, resulting in 31 *CYP2C* genes in koala, most of which were highly expressed in the liver, as determined by transcriptome analysis. Beyond diet implications, enhanced detoxification by *CYP2C* gene products may explain the ineffectiveness of some types of medicines in koalas and could thus aid in future dose optimization.

The genome provided various intriguing insights into disease pathogenesis and defence, including into the widespread, often fatal, infection with *Chlamydia pecorum*. The long contigs allowed complete assembly of various immune-related loci, such as major histocompatibility complex (*MHC*) and T cell receptor (*TCR*) gene clusters. The annotations facilitated genomic and transcriptomic analyses of koalas with and without chlamydial infections to identify putative genetic susceptibility loci and characteristic infection-associated gene expression alterations, both of which may aid vaccine design.

Finally the authors used the reference genome for demographic inferences with potential value for conservation strategies. Coalescence analyses of the latest reference genome and short-read sequencing data from two additional koalas shed light on historical population declines that have limited the genetic diversity in current populations. Moreover, mapping low-resolution single-nucleotide polymorphism (SNP) genetic diversity data onto the reference genome provided insights into inbreeding and geographical determinants of genetic diversity, which could facilitate genomically informed conservation strategies when selecting founders for rescuing or translocating populations.

Overall, this new reference genome provides rich information with numerous applications in koala disease management and conservation. The proposed genetic underpinnings of koala physiology, albeit biologically plausible, await further support for their causal roles through functional studies in model systems.

Darren J. Burgess

ORIGINAL ARTICLE Johnson, R. N. et al. Adaptation and conservation insights from the koala genome. *Nat. Genet.* https://doi.org/10.1038/s41588-018-0153-5 (2018)