Credit: Haje Jan Kamps/Alamy

Estimating spleen size from abdominal magnetic resonance imaging (MRI) in a cohort of liver steatosis enabled direct genetic association testing for SNPs in the *PDE10A* gene region; one SNP, rs3008049, was indeed found to be significantly associated with spleen size.

Finally, the researchers determined the evolutionary history of selected SNPs. The *PDE10A* SNP rs3008049 had the highest frequency in Bajau but was also found in Saluans and Han-Chinese, suggesting that rs3008049 was evolutionarily selected as a standing variant.

The results of this study exemplify the co-evolution of cultural and genetic adaptations to extreme conditions and provide evidence for local genomic selection at *PDE10A* to improve hypoxia tolerance via spleen size in response to the unique lifestyle of the sea nomads.

Michelle Trenkmann,
Associate Editor, Nature Communications.

ORIGINAL ARTICLE Ilardo, M. A. et al. Physiological and genetic adaptations to diving in sea nomads. *Cell* **173**, 569–580 (2018)

Next, the team generated *Kdm6b* loss-of-function mutants using RNA interference (RNAi). Knockdown of KDM6B at 26°C led to male-to-female sex reversal. Compared with controls, decreased expression of the testicular Sertoli cell markers *Amh* and *Sox9* and a concomitant increase in expression of the ovarian markers *Cyp19a1* and *Foxl2* after sex determination confirmed activation of the female development pathway.

Aiming to identify the target genes of KDM6B, the authors analysed six previously identified male-biased genes, two of which, *Dmrt1* and *Rbm20*, exhibited mRNA levels that were reduced by more than half in KDM6B-deficient mutants. Overexpressing *Dmrt1* in KDM6B-deficient gonads at male-producing temperatures was sufficient to rescue the knockdown, with morphology and expression patterns resembling those of controls, leading to activation of the male pathway in close to 90% of cases.

The chromatin modifier KDM6B is responsible for the demethylation of trimethylated histone H3 lysine 27 (H3K27me3), a histone mark that is associated with repressed transcription as a result of heterochromatin formation. The authors confirmed this role by immunofluorescence analysis, which showed an overall increase in H3K27me3 levels in KDM6B-deficient gonadal cells at 26°C to levels typically seen at 32°C. Furthermore, chromatin immuno-precipitation (ChIP) followed by qPCR showed that the increase in H3K27me3 levels was very prominent at the *Dmrt1* locus, to which KDM6B was strongly recruited under normal conditions.

As climate change increases temperatures across the globe, the impact on species with temperature-determined sex determination is a growing concern. Understanding the molecular and genetic mechanisms by which temperature can modulate sex determination may help ensure species survival.

Linda Koch

ORIGINAL ARTICLE Ge, C. Ye, J. et al. The histone demethylase KDM6B regulates temperature-dependent sex determination in a turtle species. *Science* **360**, 645–648 (2018)
FURTHER READING Capel, B. et al. Vertebrate sex determination: evolutionary plasticity of a fundamental switch. *Nat. Rev. Genet.* **18**, 675–689 (2017)

HUMAN GENETICS

Estimating heritability without genetic testing

Heritability, the proportion of variation in a particular trait that is attributable to genetic factors, is key to predicting disease risk. A recent study reports the use of electronic health records (EHRs), which capture a range of clinical data, as a resource for studying the heritability of traits.
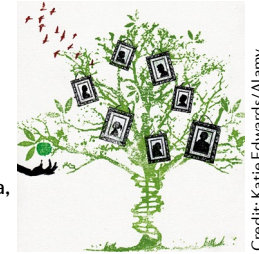
Credit: Katie Edwards/Alamy

Given that heritability underlies the predictive nature of family history for a particular disease or trait, it has been traditionally studied in family cohort studies, in particular twin studies, which are often of limited sample size. The authors recognized the opportunity provided by EHRs as a large-scale source of familial relationship data. While EHRs contain no record of genetic relatedness between patients, they do contain emergency contacts, which the team used to map the relatedness within three hospital's patient populations.

The researchers obtained 3,550,598 inpatient EHRs used at the hospitals of Columbia University Medical Center, Weill Cornell Medical Center and Mount Sinai Health System, which provided 6,587,594 emergency contacts. Of these family members, 2,191,695 were patients themselves; 1,902,827 of these provided an additional 1,588,134 emergency contacts who were next of kin. Using a newly developed algorithm for extracting relationships, called relationship inference from the electronic health record (RIFTEHR), the researchers could identify 7.4 million familial relationships across the three medical centres, without compromising patient privacy.

Clinical and genetic data were used to validate the relationships, with positive predictive values between 66% and 99% among first-degree relatives. For example, PLINK was used to estimate relatedness for 302 patients with RIFTEHR-predicted relationships from Columbia, who had consented to re-use of their genetic data. Of 172 predicted relationships, 134 were parent–offspring relationships, nearly all of which showed the expected genetic relatedness of 50%.

Based on the more than 560,000 inferred pedigrees and using only medical data from the EHRs, Polubriaginof et al. then estimated the heritability of 500 traits adjusted for age and sex using sequential oligogenic linkage analysis routines (SOLAR). The resultant heritability estimates were similar across the three centres and matched those of previously published studies. The study also resolves an ongoing debate regarding the relative heritability of plasma levels of different cholesterol types, reporting that HDL cholesterol levels are more heritable than LDL cholesterol levels.

Taken together, this study showcases the utility of (accurate) EHRs for disease genetics, even without the genetics.

Linda Koch

ORIGINAL ARTICLE Polubriaginof, F. C. G. et al. Disease heritability inferred from familial relationships reported in medical records. *Cell* https://doi.org/10.1016/j.cell.2018.04.032 (2018)