and whole-transcriptome sequencing to profile serial samples collected from patients treated with the small-molecule drug ibrutinib, which abrogates B cell receptor signalling. This experiment identified cell subpopulations with distinct transcriptomes that were preferentially expelled from the lymph node after treatment, which suggests that the drug differentially targets different CLL lineages.

In a companion study published in *Nature Communications*, Pastore, Gaiti et al. integrated DNA methylation data, histone modification maps and single-cell transcription and epigenomic profiles from healthy donor B cells and primary CLL samples to obtain an integrated epigenomic landscape of CLL. The authors found that CLL cell populations exhibit diverse histone modification profiles, which result in heterogeneity in gene expression. Unexpectedly, typically mutually exclusive activating and repressing histone modifications co-mapped. This additional level of intratumoural epigenetic diversity suggests that CLL epigenetic diversification leads to a loss of coordination across the different layers of epigenetic information. Thus, CLL populations are likely to be an admixture of cells with diverging cellular identities.

Together, both studies confirm that, at the epigenomic level, CLL lineages lose the defined hierarchy of healthy B cell populations. The remarkable diversity within each malignant cell population underscores the challenge of treating CLL. Importantly, these studies provide a ground plan of cancer evolution in vivo and demonstrate how different types of lineages respond to therapy. In the future, single-cell profiling of individual patient samples might be useful to characterize intratumoural diversity and strategize personalized therapeutic interventions.

Carolina N. Perdigoto, Associate Editor, Nature Communications

ORIGINAL ARTICLES Gaiti, F., Chaligne, R., Gu, H. et al. Epigenetic evolution and lineage histories of chronic lymphocytic leukaemia. *Nature* **569**, 576–580 (2019) | Pastore, A., Gaiti, F. et al. Corrupted coordination of epigenetic modifications leads to diverging chromatin states and transcriptional heterogeneity in CLL. *Nat. Commun.* **10**, 1874 (2019)

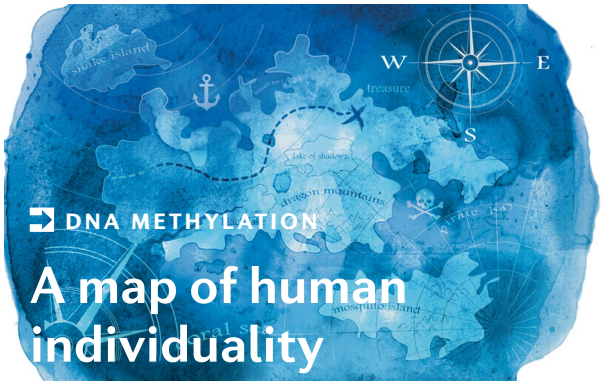
transmission, which were generally consistent with known functional importance. Variants in ribosomal RNA genes were less likely to be transmitted than those in the non-coding D-loop region, which is involved in mtDNA replication. However, higher resolution analysis of D-loop diversity in a larger population cohort showed that some poorly characterized D-loop subregions are indeed highly conserved, which might point to important molecular functions awaiting elucidation.

As the mtDNA sequences were available in the context of whole-genome sequence data, mtDNA was studied alongside nuclear DNA from the same individual. In a small subset (2.3%) of individuals, the geographical population ancestry of the mtDNA was mismatched from the nuclear DNA, which can occur due to the different segregation patterns of the ancestral mitochondrial and nuclear DNA through mixed populations. In these cases, new heteroplasmic mtDNA variants — including in several genes involved in respiration — were often under selective pressure to match the ancestry of the nuclear genome. These results were validated in an independent cohort of 40,325 individuals. Hence, there is substantial functional interplay between the nuclear and mitochondrial genomes.

Overall, the findings suggest a model whereby during female germline transmission the 1,000-fold reduction, then re-establishment, of cellular mtDNA content exerts strong selective pressure on mitochondria. This selection favours mitochondria with efficient respiration mediated by the interplay of mitochondrial protein complexes, many of which are comprised of subunits encoded separately in the nuclear and mitochondrial genomes. One implication for mitochondrial replacement therapy is that the ancestry of the oocyte donor providing the mitochondria might need to be considered for compatibility with the nuclear genome derived from the two primary parents.

Darren J. Burgess

ORIGINAL ARTICLE Wei, W. et al. Germline selection shapes human mitochondrial DNA diversity. *Science* **364**, eaau6520 (2019)



Credit: marcos alvarado/Alamy

A great body of research into the human epigenome has focused on cell type-specific, dynamic DNA methylation patterns. Now, a study in *Genome Biology* reports an atlas of systemic interindividual epigenetic variation, that is, DNA methylation that is consistent across tissues and cell types but varies between individuals. It highlights these genomic regions as a source of phenotypic variation in humans that correlates with gene expression and is associated with disease.

The team measured CpG methylation by deep whole-genome bisulfite sequencing of genomic DNA from thyroid (representing endoderm), heart (representing mesoderm) and brain (representing ectoderm) samples obtained from ten donors as part of the Genotype–Tissue Expression (GTEx) programme. This screen identified 9,926 correlated regions of systemic interindividual variation (CoRSIVs), that is, regions containing at least five CpGs at which epigenetic variation between individuals (interindividual methylation range of ≥20%) was consistent across all three tissue types. Although comprising only ~0.1% of the human genome, CoRSIVs are intercorrelated over long genomic distances, which suggests links to genome organization.

The authors used four complementary approaches to evaluate the extent to which DNA methylation at CoRSIVs is genetically mediated. These analyses revealed that ~60% of interindividual variation in CoRSIV methylation could be explained by *cis* regulatory variation, while ~40% showed no underlying genetic effect, although *trans* effects cannot be ruled out.

Importantly, DNA methylation in adipose tissue correlated with gene expression in not only the same tissue but also across two types of other tissue (skin and lymphoblastoid cells) for 645 gene-associated CoRSIVs, as determined by analysing a previous large-scale population data set. This finding suggests that CoRSIVs identified from easily obtainable sources, such as peripheral blood, could be used to infer epigenetic regulation in difficult to access tissues, such as brain, for example.

Finally, analysis of 1,319 epigenome-wide association studies based on DNA methylation showed a 37% enrichment for disease-associated CpG sites in CoRSIVs compared with control regions. CoRSIVs were not enriched for cancer but exhibited strong associations with non-cancer diseases, including several disorders related to immune function. This map of stable interindividual epigenetic variation provides new targets for studying the link between development, epigenetics and disease.

Linda Koch

ORIGINAL ARTICLE Gunasekara, C. J. et al. A genomic atlas of systemic interindividual epigenetic variation in humans. *Genome Biol.* **20**, 105 (2019)
FURTHER READING Taudt, A., Colomé-Tatché, M. & Johannes, F. Genetic sources of population epigenomic variation. *Nat. Rev. Genet.* **17**, 319–332 (2016)