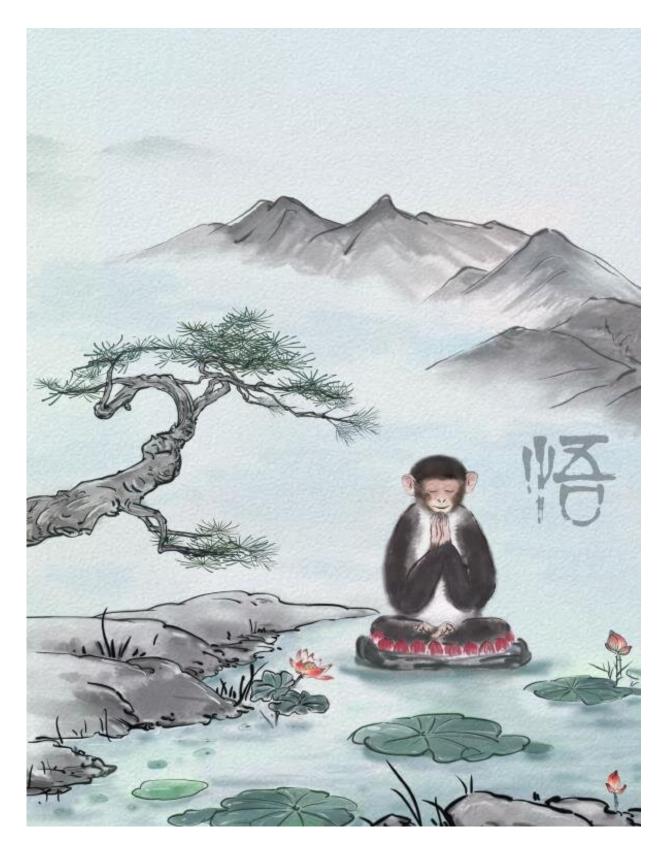


3-D genome brain study uncovers humanspecific regulatory changes during development

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The picture shows a meditating macaque, symbolizing the change of brain and



mind during primate evolution. Credit: LUO Xin et al

A team led by Prof. Su Bing from the Kunming Institute of Zoology (KIZ) of the Chinese Academy of Sciences (CAS), Prof. Li Cheng from Peking University, and Prof. Zhang Shihua from the Academy of Mathematics and Systems Science of CAS has reported the highest resolution by far of the 3-D genome of the primate brain, and demonstrated the molecular regulatory mechanisms of human brain evolution through cross-species multi-omics analysis and experimental validation. The study was published in *Cell*.

The unique pattern of human brain development stems from accumulated genetic changes during <u>human evolution</u>. Among the huge number of diverging <u>genetic changes</u>, only a small portion of the between-species changes have been functionally important. The challenge is to identify the causal changes responsible for the unique pattern of human brain development and their regulatory mechanisms. Macaque monkeys, genetically similar to humans, are the ideal model for studying the origin and developmental mechanisms of the human brain.

The genome of mammalian species including humans is about two meters long and is compiled in the nucleus with a diameter of only 10 micrometers. This nonrandom compilation is characterized by organized three-dimensional (3-D) distribution, which is important for cell proliferation and differentiation during development. Recently, the invention of whole-genome chromosomal structure capture technology (referred to as Hi-C) provides a great opportunity for dissecting the finetuned organization of the genome during brain development.

In this study, the researchers conducted cross-species analyses of brain



3-D genomes through cross-disciplinary collaboration.

They first constructed a high-resolution 3-D chromatin structure map of the macaque fetal brain using the Hi-C technique. Reaching a 1.5 kb resolution, this Hi-C map represents the highest resolution of primate brains so far achieved, and it has become a useful omics dataset for revealing the 3-D genome organization in detail. Meanwhile, the researchers generated a transcriptome map, a chromatin open region map and a map of the anchor protein CCCTC-binding factor (CTCF).

Based on these multi-omics data, the researchers constructed for the first time a fine map of the chromatin structure of the macaque fetal brain and identified the chromatin structure in different scales, including compartments, topologically associating domains (TADs) and chromatin loops. They also identified regulatory elements in the genome such as enhancers.

Using published human and mouse brain Hi-C data, they then performed a cross-species comparisons, and discovered many human-specific chromatin structural changes, including 499 human-specific TADs and 1266 human-specific loops. Notably, the human-specific loops were shown to be enriched with enhancer-enhancer interactions, representing the origin of a mechanism for fine-tuning brain development during human evolution.

Based on the analysis of single-cell transcriptome data on human brain development, the researchers observed that these human-specific looprelated genes are highly expressed in the subplate lamina, a transient zone of the developing brain critical for neural circuit formation and plasticity. The subplate lamina had been found to show an extradentary expansion compared to that of the macaque and mouse, and is about four times the thickness of the cortical plate. The subplate starts to decrease after birth and eventually disappears, and little is known about this



transient zone. This finding provides the first evidence for the key role of the subplate in forming human-specific brain structures during development.

In addition, the researchers discovered that many human-specific mutations (e.g., point mutations and structural changes) are located in the TAD boundary and loop anchor regions, which may lead to the origin of novel binding sites of transcriptional factors and human-specific chromatin structures.

The researchers studied an example involving the EPHA7 gene, which is highly expressed in the subplate and is critical for neuronal dendrite development. The human-specific point mutations of EPHA7 lead to the formation of human-specific enhancers and loops. Through an experiment involving enhancer knockout in cell lines, they proved that human-specific EPHA7 enhancers can cause regulatory changes in EPHA7 expression and affect dendrite <u>development</u>.

This study sheds new light on the genetic mechanisms of human brain origin and serves as a valuable resource for 3-D <u>brain</u> genomes.

More information: Xin Luo et al. 3D Genome of macaque fetal brain reveals evolutionary innovations during primate corticogenesis, *Cell* (2021). DOI: 10.1016/j.cell.2021.01.001

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