Website address:
https://www.gesundheitsindustrie-bw.de/en/article/press-release/using-ai-retrace-evolution-genetic-control-elements-brain

Using AI to Retrace the Evolution of Genetic Control Elements in the Brain

Artificial intelligence allows tracing the evolution of genetic control elements in the developing mammalian cerebellum. An international research team led by biologists from Heidelberg University as well as the Vlaams Instituut voor Biotechnologie and KU Leuven (Belgium) has now developed advanced AI models that can predict the activity of these elements based solely on their DNA sequence. Using these models, the scientists were able to retrace the evolutionary changes in the control programs, also identifying those that are specific to the human lineage.

Genetic control elements are DNA sequences that determine where and when genes are switched on. Changes in the activity of these elements can drive evolutionary innovations – such as the expansion of the brain. One brain region that notably expanded during human evolution is the cerebellum, which, beyond its role in movement and balance, also contributes to cognition, emotion, and language. "Tracing the evolution of genetic control elements has long been challenging due to their rapid evolutionary turnover and our limited understanding of how their activity is encoded in their DNA sequence," explains Prof. Dr Henrik Kaessmann, a research group leader at the Center for Molecular Biology of Heidelberg University (ZMBH).

To close this knowledge gap, the researchers made use of advances in artificial intelligence. "Customized tools for the AI-based analysis of comprehensive and complex datasets in the life sciences have allowed us to decode the sequence grammar and hence the genetically coded activity profiles of these control elements," states Prof. Dr Stein Aerts, a computational biologist at the Vlaams Instituut voor Biotechnologie and KU Leuven who co-led the research studies with Prof. Kaessmann.

The researchers used modern sequencing technologies to map the activity of these elements in individual cells in the developing cerebellum of human, bonobo, macaque, marmoset, mouse, and opossum. Using this unique dataset, they trained models based on machine learning in order to be able to predict control element activity directly from the respective DNA sequence. These AI models were not only able to model the activity of these elements in the six species studied, but also to accurately predict the activity across other mammals. "This goes to show that the sequence rules that define genetic control elements in cerebellar cell types have been highly conserved throughout mammalian evolution," explains Dr Ioannis Sarropoulos, formerly a doctoral student in Prof. Kaessmann's group and co-first author of a paper that has been published on the latest research findings – alongside Dr Mari Sepp, a former Kaessmann lab postdoc, and doctoral candidate Tetsuya Yamada.

Building on these findings, the scientists leveraged the AI models' ability to recognize conserved sequence rules to predict the activity of control elements in 240 mammalian species. For every human element, the researchers succeeded in identifying whether the corresponding sequence is active in other mammals. This allowed them to reconstruct the evolutionary history of human regulatory programs at high resolution and identify those that likely contributed to key evolutionary innovations in the human cerebellum. For example, they discovered a new control element near the gene *THRB*, which encodes a thyroid hormone receptor found in all vertebrates. This new element has enabled this gene to also operate in cerebellar stem cells. According to Prof. Kaessmann, this could have contributed to the evolutionary expansion of the human cerebellum. "That an evolutionarily ancient gene can be repurposed for novel functions is a key mechanism by which evolution drives innovation," emphasizes the Heidelberg molecular biologist.

In addition to the teams from Heidelberg and Leuven, researchers from Göttingen and Leipzig as well as Hungary and the United Kingdom contributed to the study. The project was funded by various organizations and foundations, including the European Research Council, the European Molecular Biology Organization, and the Simons Foundation. The results of the study were published in the journal "Science".

Original publication

I. Sarropoulos, M. Sepp, T. Yamada, P.S.L. Schäfer, N. Trost, J. Schmidt, C. Schneider, C. Drummer, S. Mißbach, I.I. Taskiran, N. Hecker, C. Bravo González-Blas, R. Frömel, P. Joshi, E. Leushkin, F. Arnskötter, K. Leiss, K. Okonechnikov, S. Lisgo, M. Palkovits, S. Pääbo, M. Cardoso-Moreira, L.M. Kutscher, R. Behr, S.M. Pfister, S. Aerts, and H. Kaessmann: The evolution of gene regulation in mammalian cerebellum development. Science (published online 29 January 2026).
DOI: 10.1126/science.adw9154

Press release

27-Jan-2026
Source: Heidelberg University

Further information

- Heidelberg University