

# Rewiring of gene regulation across 300 million years of evolution

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As published today in *Science*, researchers from Cambridge, Glasgow and Greece have discovered a remarkable amount of plasticity in how transcription factors, the proteins that bind to DNA to control the activation of genes, maintain their function over large evolutionary distances.

The text books tell us that [transcription factors](#) recognise the genes that they regulate by binding to short, sequence-specific lengths of DNA upstream or downstream of their target genes. It was widely assumed that, like the sequences of the genes themselves, these transcription factor binding sites would be highly conserved throughout evolution. However, this turns out not to be the case in mammals.

The authors traced the evolution of [gene regulation](#) by comparing the binding of evolutionarily conserved transcription factors in the genomes of five vertebrate species - human, dog, mouse, short-tailed opossum and chicken - spanning 300 million years.

In all tested species, the transcription factors CEBPA and HNF4A are master regulators of liver-specific genes. By mapping the binding of CEBPA and HNF4A in the genomes of each species and comparing those maps, they found that in most cases neither the site nor the sequence of the transcription factor binding sites is conserved, yet despite this, these transcription factors still manage to regulate the largely conserved [gene expression](#) and function of liver tissue.

Paul Flicek, leader of the Vertebrate Genomics Team at EMBL-EBI, an outstation of the European Molecular Biology Laboratory, and coauthor on the paper said "The [evolutionary changes](#) in transcription factor binding in the five species have left clues that we can use to explain how function is preserved but not necessarily sequence. What we have learnt is that although the transcription factors regulate similar target [genes](#) in all five species, the binding events underpinning this regulation have not been conserved as the species diverged."

"By studying changes in transcription factor binding, we can understand the evolution of gene regulation," said Duncan Odom from Cancer Research UK Cambridge Research Institute and coauthor on the paper. He continued: "Differences in gene regulation are central to explaining differences between species, and gene misregulation is a key causative factor in diseases like cancer."

The results reveal that sequence conservation is not the whole story when it comes to maintaining tissue-specific gene regulation.

**More information:** Schmidt, D., Wilson, M.D., Ballester, B., Schwalie, P.C., Brown, G.D., Marshall, A., Kutter, C., Watt, S., Martinez-Jimenez, C.P., Mackay, S., Talianidis, I., Flicek, P., Odom, D.T. Five vertebrate ChIP-seq reveals the evolutionary dynamics of transcription factor binding. *Science*, 8 April 2010. (Published online in *Science Express Reports*, [DOI:10.1126/science.1186176](https://doi.org/10.1126/science.1186176) ).

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