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EVOLUTION

Talking about FOXP2

The use of language is a uniquely human characteristic; however, the molecular changes that led to the evolution of human speech are largely unknown. Konopka *et al.* now show that human-specific changes in the amino acid sequence of forkhead box P2 (FOXP2), a transcription factor that is important for speech, alter the neuronal expression of a panel of genes, providing insight into the contribution of this protein to the development of speech.

A specific role for FOXP2 in the evolution of speech was suggested by the appearance of two amino acid substitutions in the protein after the separation of the human and chimpanzee lineages, coinciding with the period during which speech is thought to have first appeared. However, until now the consequences of these amino acid changes for the protein's activity were unknown.

To compare the properties of human and ancestral (chimpanzee) FOXP2 the authors expressed each form of the protein in human neuronal cell lines that lacked endogenous FOXP2 and carried out whole-genome microarray analysis and quantitative PCR following reverse transcription (qRT-PCR) to examine gene expression. 116 genes were up- or downregulated to a greater extent by human FOXP2 than by chimpanzee FOXP2. Furthermore, many of these genes were differentially expressed in tissues taken from the caudate nucleus, frontal pole and hippocampus of human and chimpanzee brains.

To determine how the amino acid substitutions in FOXP2 lead to differential effects on gene transcription, the authors examined the short promoter regions of eight of the target genes affected. Six of these were differentially transactivated by human FOXP2 and chimpanzee FOXP2.

This study suggests that the changes in FOXP2 amino acid sequence that occurred during human evolution have substantial consequences for the protein's effects on brain gene expression. The genes affected included some that are linked to motor aspects of speech or to brain and craniofacial development, indicating that FOXP2 might regulate the development of both neural and physical structures needed for human speech. This work complements recent findings that insertion of the human FOXP2 amino acid substitutions into mouse FOXP2 modifies cortico-basal ganglia circuits and vocalization (see Further reading). Additional work will be needed to determine how the genes differentially regulated by human FOXP2 contribute to our capacity to use language.

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ORIGINAL RESEARCH PAPER Konopka, G. *et al.* Human-specific transcriptional regulation of CNS development genes by FOXP2. *Nature* **462**, 213–217 (2009)

FURTHER READING Enard, W. *et al.* A humanized version of Foxp2 affects cortico-basal ganglia circuits in mice. *Cell* **137**, 961–971 (2009)

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