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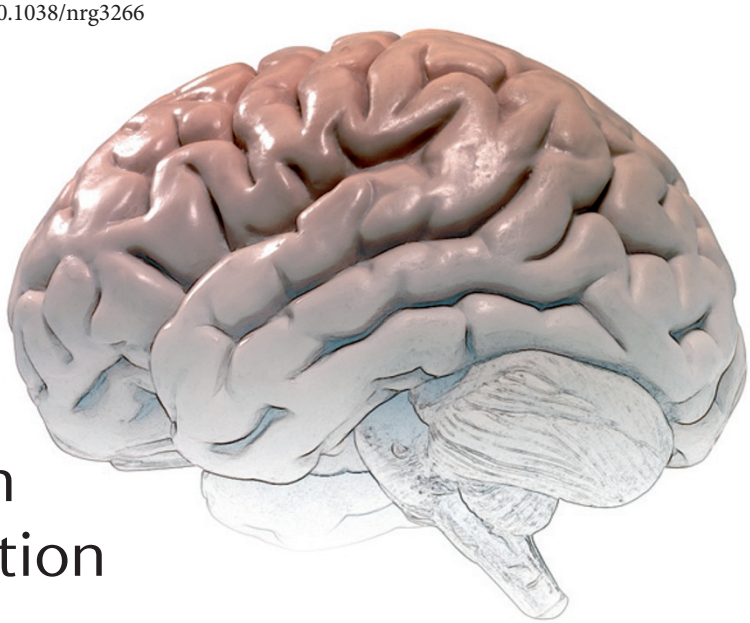

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GENOME EVOLUTION

Functional antagonism and human brain evolution

Bursts of gene duplication have occurred in the human and great-ape lineages, and human-specific duplications are enriched in genes expressed during brain development. However, the function of these genes in brain development is currently unknown. Two studies now show an intriguing mechanism by which a human-specific duplication may have had a role in human brain evolution.

Both studies examined the SLIT–ROBO Rho GTPase-activating protein 2 (*SRGAP2*) gene, which is involved in cortical development and has been highly conserved over mammalian evolution. Using fluorescent *in situ* hybridization (FISH) and high-coverage sequencing, Dennis and colleagues confirmed that *SRGAP2* has been partially duplicated three times in the human lineage. The ancestral form of the gene, *SRGAP2A*, was first duplicated approximately 3.4 million years ago (giving rise to *SRGAP2B*), and this was then followed by two later duplications (giving rise to *SRGAP2C* and *SRGAP2D*) approximately 2.4 million and 1 million years ago.

SRGAP2A contains three functional domains, one of which results in protein dimerization. Interestingly, Charrier and colleagues found that the SRGAP2C protein (which contains most of the dimerization domain, despite being only partially duplicated) is able to dimerize with itself or with SRGAP2A *in vitro* and that co-expression of SRGAP2C efficiently blocks the ability of SRGAP2A to induce filopodia projections from COS7 cells. Furthermore, the authors found that co-expression of SRGAP2C in mouse neurons induced neoteny of spine maturation, resulting in increased dendritic spine density and longer spines. This is a similar phenotype to that observed in the mouse *SRGAP2* knockout *in vivo*. Their results suggest that SRGAP2C antagonizes SRGAP2A, and thus SRGAP2C expression has long-term effects on spine density and morphology. The authors speculate that expression of SRGAP2C may increase the number of synaptic inputs that human neurons can receive and integrate, allowing for more flexibility in input integration and information processing.

> “human-specific duplication of *SRGAP2* antagonizes the ancestral gene function”

Therefore, these studies propose a mechanism whereby the human-specific duplication of *SRGAP2* antagonizes the ancestral gene function. This change may have an important influence on cognition, learning and memory. Notably, the time of the duplication event corresponds to a time in human evolution that is associated with the expansion of the neocortex and with changes in behaviour, such as the use of stone tools.

Bryony Jones

ORIGINAL RESEARCH PAPERS Dennis, M. *et al.* Evolution of human-specific neural *SRGAP2* genes by incomplete segmental duplication. *Cell* **149**, 912–922 (2012) | Charrier, C. *et al.* Inhibition of SRGAP2 function by its human-specific paralogs induces neoteny during spine maturation. *Cell* **149**, 923–935 (2012)