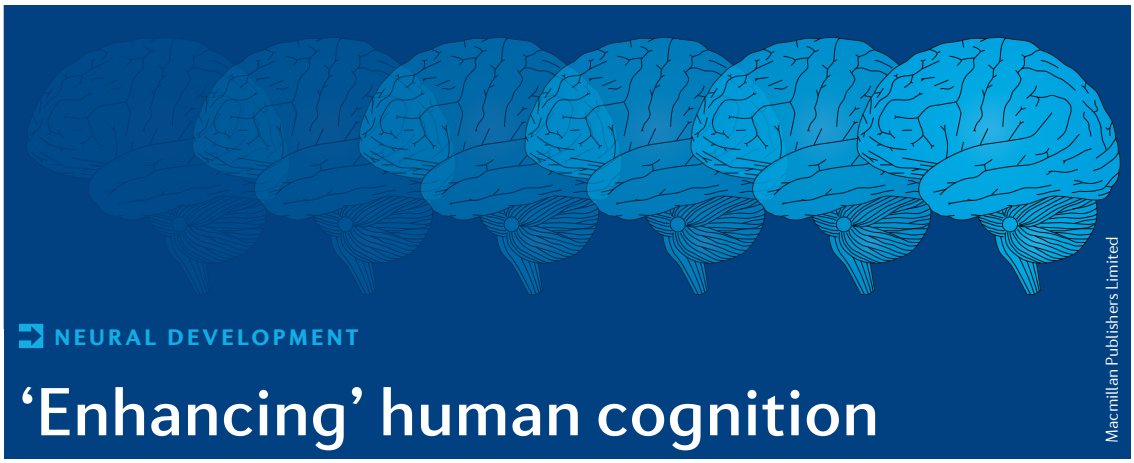
Nature Reviews Neuroscience | Published online 01 Feb 2018; doi:10.1038/nrn.2018.11



‘Enhancing’ human cognition

> HGE-mediated regulation of *FGFR2* expression could contribute to human cortical expansion by promoting neuronal progenitor proliferation

The emergence of advanced cognition in humans has been made possible because of the evolutionary expansion of the cerebral cortex. Changes in the genetic regulation of neurogenesis in the developing brain are thought to have been crucial for this expansion, but the mechanisms not well understood. Here, de la Torre-Ubieta *et al.* show that human cortical neurogenesis and, by extension, cortical expansion and cognition are partly controlled by certain genetic regulatory elements, known as human-gained enhancers (HGEs), that previous studies identified as showing increased activity in the human lineage.

Gene expression is regulated in part by non-coding regulatory elements, such as enhancer and promoter sequences, within the genome. To investigate the regulation of the genes controlling corticogenesis, the authors focused on two areas of fetal neocortex: the progenitor-rich germinal zone (GZ) and the neuron-enriched cortical plate (CP). They integrated chromatin-accessibility data, RNA sequencing data and chromatin interaction data to build a picture of enhancer activity and gene expression in the developing human brain. They observed a highly significant correlation between regions of high chromatin accessibility and expression across a set of genes involved in neural development and neurogenesis. They noticed that many of these differentially accessible regions overlap with HGEs.

The target genes of HGEs active during cortical development were found to regulate neural progenitor proliferation and were enriched specifically in outer radial glia (oRGs). This is important because oRGs are present in higher numbers in humans relative to other species and may be crucial for elaboration of the human and primate cerebral cortex. Furthermore, several genes regulated by HGEs in the fetal brain were also contained in a list of genes uniquely expressed in oRGs, suggesting that this cell type has become more highly regulated by HGEs during progression of the human lineage and elaboration of the human cerebral cortex. In addition, HGE-regulated genes were more enriched in neural progenitors and glia in the outer subventricular zone, an area that is substantially larger in humans compared with other primates.

The gene encoding fibroblast growth factor receptor 2 (FGFR2) has been suggested to be regulated by HGEs and in mice, FGFR2 is involved in regulating neural progenitor proliferation. Here, the authors identified a GZ-enriched HGE that was predicted to functionally interact with the human *FGFR2* gene. Deletion of this HGE in undifferentiated primary human neuronal progenitor cells decreased *FGFR2* expression and reduced cell self-renewal, indicating that HGE-mediated regulation of *FGFR2* expression could contribute to human cortical expansion by promoting neuronal progenitor proliferation.

Many genetic variants that are associated with an increased risk of neuropsychiatric disorders such as schizophrenia occur in non-coding regions. Interestingly, these genetic loci were enriched in regions of open chromatin in the germinal zones relative to the cortical plate, suggesting that genes regulated by enhancers active during neurogenesis (which might include HGEs) contribute to the pathophysiology of these conditions.

Together, these findings suggest that, in the developing human brain, HGEs preferentially regulate genes associated with human-specific cortical expansion — and in particular, oRG proliferation. These findings might provide insight into the mechanisms underlying some neurodevelopmental and neuropsychiatric disorders.

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ORIGINAL ARTICLE de la Torre-Ubieta, L. *et al.* The dynamic landscape of open chromatin during human cortical neurogenesis. *Cell* **172**, 289–304 (2018)