# Scaling corticogenesis across evolution

## Genomic change in TKTL1 could explain increased neurogenesis in modern humans.

**By Brigitte Malgrange and Laurent Nguyen**

The neocortex is an evolutionarily advanced brain structure responsible for cognitive abilities. It has expanded and functionally complexified across the mammalian clade (*1*). It is considered that humans' extraordinary cognitive abilities rely not only on the size and thus the number of neurons but also on the intricate cytoarchitectonic of their neocortex. The neocortical blueprint relies on the tight coordination of fundamental cellular and molecular events. The neocortex's expansion and folding have been widely attributed to the existence of basal (bRG), also named outer radial glia (oRG). These progenitors generate most cortical projection neurons, and their number strikingly increases in gyrencephalic mammals, such as primates and ferrets. Among the hominids, humans have a neocortex that contains around twice the number of neurons and is larger than the chimpanzees and bonobos (*2*). The emergence of human-specific genes has contributed to the expansion and rapid evolution of the cerebral cortex (*3*). Still, recent anthropological data obtained from skull endocasts suggest that Neandertal, one of our closest extinct relatives, shares comparable brain volume with modern humans (*4*). Whether this reflects an equivalent amount of white and grey matter and thus a similar production of the corresponding number of cortical neurons remains unknown. While we have a limited understanding of the contribution of the evolutionary changes that shape the modern human brain, a recent comparison of the Neanderthal and modern human genomes identified specific nucleotide changes in genes that may have an essential role in the brain evolution and the acquisition of novel cognitive capabilities.

On page XX of this issue, Pinson et al. find that expression of the modern variant of human TKTL1 increases the number of bRGs, thereby the output of upper layer projection neurons (uCP, figure 1), compared to the neandertal's one. This specific feature of modern brain neurogenesis could contribute to a difference in cognition with extinct archaic humans.

Because human brain fossil records are rare, efforts to understand the evolution of the neocortex at a cellular and molecular level have been limited to comparing living species—an approach known as "evo-devo" (*5*). Observations of the developing neocortex in humans, nonhuman primates, carnivores, and marsupials reveal how differences in neural progenitor cell populations can result in variable size and shape of neocortices.

Most current knowledge about the cellular and molecular mechanisms of neocortical development is based on experimental analysis of mouse models, whose neocortex exhibits key features general to mammals, including a six-layered organisation and regionalisation into specialized areas. However, one limitation of this animal model to study human corticogenesis is its small size and lack of folded surface. Increases in neocortical surface and brain volume in gyrencephalic mammals result from expanding progenitor cells in the outer subventricular

zone (OSVZ) during development (*6-8*). To what extent such cellular mechanism has progressively been established during the evolution of the genus Homo remains unknown. The authors have elegantly explored this question by combining analyses of human cerebral organoids with in vivo studies of the mouse, ferret, and human brains.

**What makes the modern human brain unique?** To address this critical question, Pinson et al. exploited one genetic difference identified between modern and archaic humans, the Neandertals. They identified one amino acid substitution in the *Transketolase-like 1 (TKTL1)* gene of modern humans (hTKTL1) as compared to the corresponding archaic human sequence (aTKTL1). *TKTL1* encodes for a key enzyme in the non-oxidative branch of the pentose phosphate pathway (PPP). TKTL1 has been mainly studied for its contribution to tumour metabolism, acting as an enhancer of aerobic glycolysis (*9*). Interestingly, *TKTL1* is also expressed in the germinal compartment of the human but not the rodent neocortex, and a *TKTL1* variant has recently been associated with neural tube defects (*10*).

To decipher the role of TKTL1 during embryonic neurogenesis, the authors took advantage of the mouse brain, which lacks expression of Tlk1 and overexpressed hTKTL1 or aTKTL1. They demonstrated that only hTKTL1 selectively promotes the proliferation and expansion of bRG in the mouse embryonic brain. Surprisingly, *hTKTL1* mRNA is also abundantly expressed in apical radial glia (aRG), while its overexpression does not affect this cell population. Moving to the gyrencephalic ferret neocortex, which endogenously expresses aTKTL1, Pinson et al. also showed that the bRG cell population was increased when hTKTL1 was overexpressed. Finally, disrupting hTKTL1 expression in human neocortical organotypic slices reduces bRG abundance, while gene-edited hESCs expressing aTKTL1 exhibit reduced bRG and neuron generation.

**What makes hTKTL1 functionally distinct from aTKTL1?** Pinson et al. showed that hTKTL1 acts via the PPP, an essential pathway for acetyl-CoA generation and fatty acid synthesis. Whether aTKTL1 plays the same role has not been determined. Here, they showed that overexpression of hTKTL1 but not aTKTL1 significantly increased acetyl-CoA levels in bRGs. Altogether, the results supported that hTKTL1 promotes the amplification of bRGs, a cell population characterised by long basal processes that require fatty acid synthesis. This mechanism could represent one crucial driver of brain evolution between ancestral and modern humans.

Altogether, the work of Pinson et al. shed light on a critical variant that may have functional consequences on the brain structure and behavior of modern humans. This observation also comes together with the recent and debated finding that reintroducing an ancestral amino acid substitution in the splice factor NOVA1 drastically alters the development of human brain organoids (*11*). Together, these observations likely represent only the emerged tip of the iceberg but open the exciting path to discover more specific evolutive changes that shaped the modern human brain and may also help us predict the next steps of its evolution.

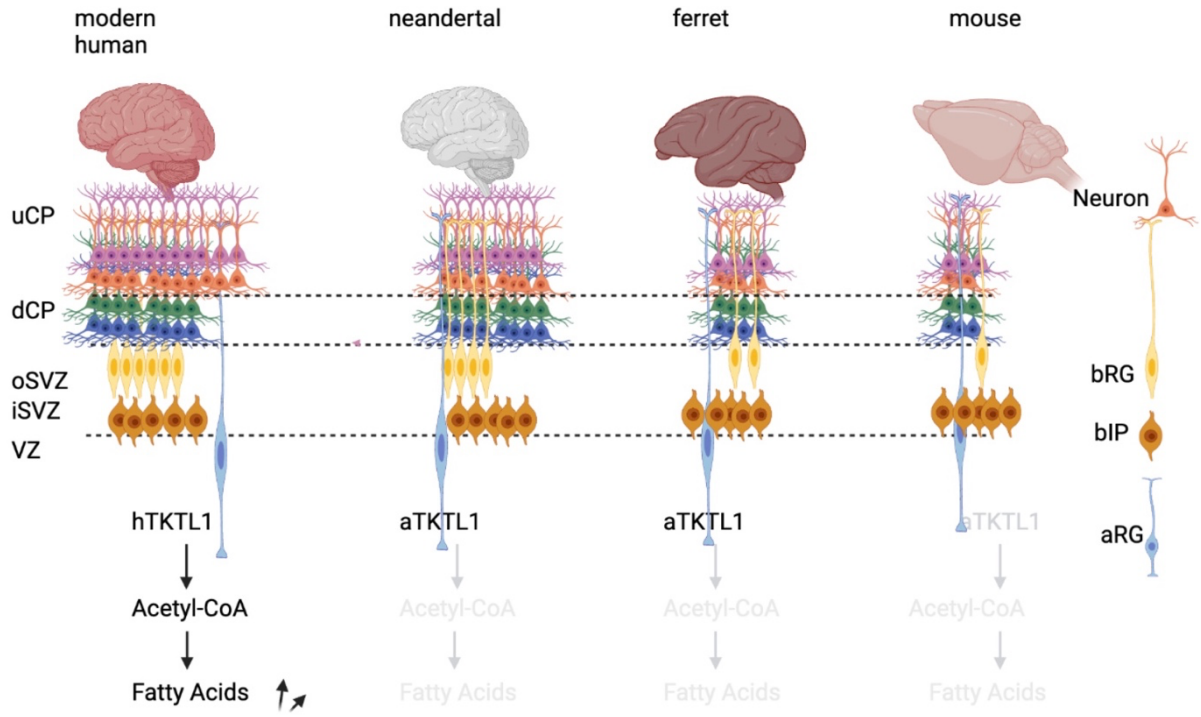


**Figure 1** hTKTL1 single lysine-to-arginine amino acid substitution in modern humans has a specific role in the basal radial glial cell population, consequently impacting the upper-layer neuronal population. uCP = upper cortical plate, dCP = deed cortical plate, SVZ = subventricular zone, VZ= ventricular zone, bRG = basal radial glia, bIP= basal intermediate progenitors and aRG= apical radial glia.

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