How to make an ape brain

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Many genes and genetic mechanisms contributed to the evolution of humans from a common primate ancestor. Emergence of the ape brain was apparently facilitated by a retrotransposed gene duplicate that acquired brain-specific expression and functions affecting the neurotransmitter glutamate.

From an anthropocentric perspective, the origin of humans is one of our greatest unsolved mysteries. There are many approaches to explaining the human phenomenon, each with its own problems and prospects. One approach is to compare our genomes and genes with those of closely related species, hoping to identify changes that might explain unusual features of the human condition[1]. Hence, there was much excitement about the recent release of the draft sequence of the chimpanzee genome and anticipation about what one might find in comparisons with the human genome[2]. Detailed comparisons of single homologous chimpanzee and human chromosomes[3], and preliminary reports regarding the whole genome[4], indicate that the situation will be far from simple and that we need to search for many needles in a very large haystack of differences. Thus, an important parallel approach is to study select candidate genes. It is also logical to focus on genes that seem to be important in anatomic and physiological systems that show the most unusual human features, including the skin, musculoskeletal system, female reproductive system, immune response and brain. Only in the last decade or so have a number of such candidate genetic differences emerged. Examples run the gamut from outright gene inactivations or deletions to

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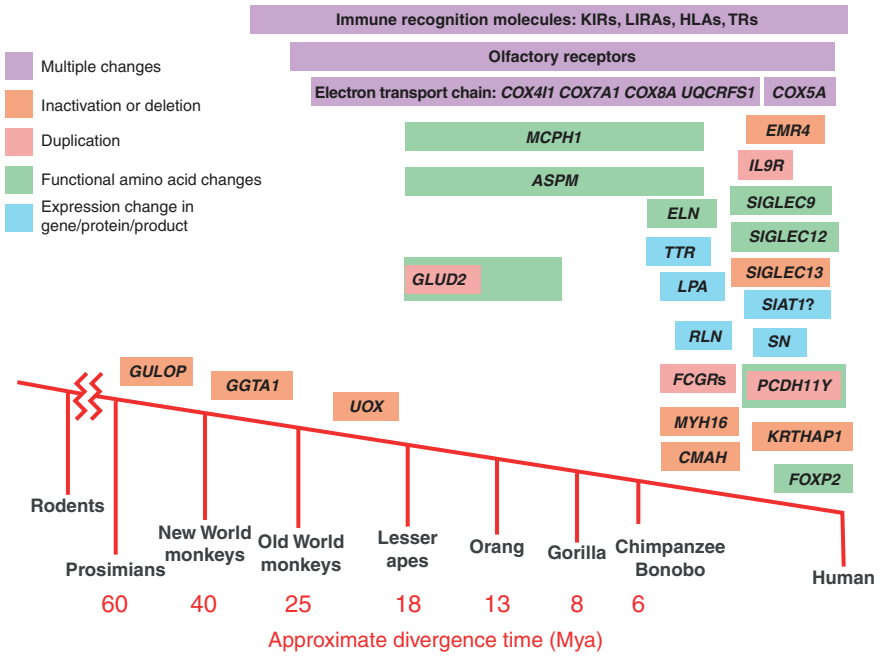

Figure 1 An anthropocentric view of primate gene evolution. From the limited data available, many genes underwent substantial changes in the primate lineage leading to humans. As the examples presented here indicate, these changes range from complete gene deletions to subtle changes in amino acid sequences altering function to changes in expression levels of the encoded protein or its enzymatic product. There are many more examples in the literature of human-specific changes in gene expression, mostly defined at the mRNA level. *GLUD2* is an unusual example of a gene that emerged as an intronless duplicate of *GLUD1* by retrotransposition of its mRNA, achieved specialized expression in the brain and then acquired multiple amino acid changes to facilitate its functioning in the brain. Along with changes in other molecules, such as *APSM*, *MCPH1* and multiple components of the mitochondrial electron transport chain, the emergence of GLUD2 probably facilitated encephalization and specialization of the ape brain, forming a vital basis for the later emergence of the human brain. General facts about most gene names can be found at http://www.gene.ucl.ac.uk/nomenclature/ and literature references at PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi).

changes in amino acids essential to function to alterations in expression patterns of otherwise similar genes (**Fig. 1**).

Although much attention is focused on the genetic differences between humans and our closest evolutionary relatives (chimpanzee, bonobo, gorilla and orangutan—the great apes; **Fig. 1**), one must not forget that this lineage arose from deeper phylogenetic roots that were also quite specialized relative to other mammals—the order of primates in general and the Old World primates (OWPs) in particular. As Goodman, Grossman and colleagues emphasize[5], it may be just as important to define genetic changes specific to the emergence of the OWPs, without which the final specializations that gave rise to humans would not have had any place to take root. In this regard, it is of note that the vaunted 'big brain' of humans arose on a background of substantial encephalization and specialization that was already ongoing in OWPs. In this context, recent data indicate that several genes known to be important in the structure and function of the human brain have been undergoing positive darwinian selection during and since the emergence of the OWPs, such as those encoding several mitochondrial electron transport chain proteins[5] and determinants of brain size, such as *ASPM*[6–8] and microcephalin (*MCPH1*; ref. 9). On page 1061 of this issue, Burki and Kaessmann[10] introduce another player which specifically affects the brain metabolism of the key neurotransmitter glutamate. The story is made all the more fascinating by the fact that it involves the 'birth' of a new gene in the ape lineage.

Two GLUDs are better than one

Glutamate dehydrogenase is an enzyme that catalyzes the reversible oxidative deamination of glutamate to α-ketoglutarate using NAD or NADP as cofactors. Before 1994, only one mRNA for this enzyme activity was known, encoded by an evolutionarily conserved, intron-containing, widely expressed 'housekeeping' gene called *GLUD1*. Shashidharan *et al.*[11] then discovered a new mRNA that arose from an intronless duplicate of this gene, called *GLUD2*, and noted it to be selectively expressed in the retina, testis and brain. Although the concept of gene duplication leading to the birth of new genes is well established, such new genes typically arise from small- and large-scale genomic duplication or gene conversion events. In contrast, Burki and Kaessmann[10] show that *GLUD1* underwent duplication by a pathway that more commonly generates processed pseudogenes. Thus, a processed mRNA for *GLUD1* became retrotransposed and reinserted itself into the genome as an intronless copy (*GLUD2*), which acquired a new brain-specific expression pattern and then a series of amino acid sequence changes, leading to the optimization of its functional capabilities in the brain. These functional changes include resistance to the high GTP levels in the brain, a markedly increased activity dependence on the allosteric activators ADP and L-leucine, and the ability to function at relatively low pH. The authors suggest that these features allow instant activation of the enzyme in the brain when there is high frequency firing of neurons.

From the anthropocentric perspective, it is particularly interesting that this event occurred just before the emergence of the ape lineage (Old World monkeys do not have a *GLUD2* gene; **Fig. 1**). Furthermore, Burki and Kaessmann[10] use various methods of phylogenetic analysis to show that the pattern of amino acid changes in GLUD2 since the duplication event show the signature of positive darwinian selection and that some of them are probably associated with the previously known differences in the biochemical properties of GLUD1 and GLUD2.

Productive insertions

Such processed pseudogenes seem to be peculiar to mammalian genomes, probably because such genomes have a high content of LINE elements, which provide the reverse transcriptase activity to generate the cDNAs before insertion[12,13]. The occurrence of such processed pseudogene insertions is rather common. For example, comparisons of the chimpanzee and human genomes indicate that ~200 such insertions have occurred in each of the lineages since their last common ancestor ~6 million years ago (Mya). Correcting for the current coverage of chim-

panzee-human alignments and the time of divergence, the estimated rate of formation of processed pseudogenes is 40–60 per Mya (D. Torrents, personal communication, for the Chimpanzee Genome Sequencing Consortium). Most such processed pseudogenes are 'dead on arrival', however, because of copying errors that occur during their creation. Even those that initially contain an intact open reading frame are not typically expressed, because they lack promoters. It is reasonable to speculate that *GLUD2* happened by chance to insert adjacent to brain-specific promoter element(s), which then allowed selective pressure to support and enhance its continued expression. Partial deficiency of glutamate dehydrogenase activity has been found in individuals with various neurodegenerative disorders[11], and excitotoxic neuronal death can be caused by accumulation of excess glutamate[14]. Given that *GLUD2* is an ape-specific gene, it is difficult to test its importance in the standard rodent models. As it is located on the X chromosome, however, there is a reasonable likelihood that somewhere in the human population are males who carry *GLUD2* mutations. Finding such individuals and studying their phenotypes would be a large step towards understanding the importance of GLUD2 in human brain evolution and function.

Thus, in addition to losing their tails, our ape ancestors seem to have been selected for multiple genetic modifications that favored the emergence of their specialized brains. The current work[10] provides yet another piece to this part of the complex puzzle of human origins. In the final analysis, genes alone cannot explain the human brain. We must remember that the ape brain in general and the human brain in particular owe many of their sophisticated abilities to a intimate synergy between nature (genes) and nurture (environment). Thus, even if we eventually find all the needles in this haystack, the human mind will ultimately be explained only as "Nature via Nurture"[15].

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