E&EB 122: Introduction to Ecology and Evolutionary Biology
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By submitting this essay, I attest that it is my own work, completed in accordance with University regulations. —Sarah Foote

Paper Title: Evaluating the influence of evolution on human brain size

by Sarah Foote

**Abstract**

The primate lineage leading to humans has evolved brains that are dramatically large relative to body size in comparison to other mammals. I suggest that environmental factors of the areas inhabited by Hominids were more likely than social dynamics to have provided the key to initial brain expansion. The fossil record provides evidence of increasingly encephalized Hominids both in areas of greater climatic variation and along shorelines. However, while positive selection for brain size along the primate lineage leading to humans is relatively undisputed, it is unclear whether directional selection is still acting to increase human brain size. Analysis comparing the evolutionary rates of genes highly expressed in cortical and subcortical brain structures indicates that the brain is evolving more slowly than other areas of the body. Coefficients of variance calculated for the size of the brain and other organs also indicate that stabilizing selection is currently a dominant influence on brain size. Analysis of the evolution of two genes specifically implicated in brain growth is inconclusive –MCPH1 shows the marks of stabilizing selection, while ASPM has been under positive selection along the most recent Homo line. Evidence indicating that ASPM is under recent positive selection is particularly noteworthy because ASPM plays a unique role in development of the cerebral cortex. The folded structure of the cerebral cortex means that increases in cortical surface area can occur without generating proportional increases in volume. Thus, positive selection could act on cortical size without

producing a significant variation in measurable brain volume. For this reason, I propose that the evolution of the cerebral cortex should to be examined independently of subcortical brain structures before we draw the conclusion that brain size of modern humans is under stabilizing selection.

**Introduction**

One of the main features distinguishing human evolution from the evolution of other animals is the dramatic growth of the brain. The human brain is not necessarily the largest in the animal kingdom by direct volume comparison - the brains of many large organisms, such as the sperm whale and elephant, literally have more mass. However, the 'encephalization quotient', a measure of brain size as a proportion of body size, reveals that humans are more highly 'encephalized' than other animals. As encephalization is highly correlated with intelligence, understanding the evolution of brain size in humans is key to understanding the evolution of higher intelligence (McDaniel 2005). However, brain size is not the only important variable – the organization of the brain is also important. In particular, mammalian brain evolution is distinguished by the development of a cerebral cortex with extremely large surface area. In humans, a relatively enlarged cerebral cortex has increased the capacity for language development, refined social interaction, and tool-making. Thus, if we are examining human brain expansion for the purpose of understanding increased intelligence, we must focus our attention on the evolution of the cerebral cortex.

The identity of the original trigger of cortical expansion is still under debate. The classic explanation cites tool use and refined social interaction as key factors influencing the expansion of the brain (Jerison 1973). Individuals with increased tool-making and social skills conferred by a larger brain would have enjoyed reproductive advantages, passing on their genes at a higher

rate. However, the idea that tool-making and social capacity served as triggers of brain evolution is questionable. While tool-making and social skills could potentially feed back to improve brain function, a sophisticated brain would have been necessary for those skills to develop in the first place. This observation begs the question of whether the development of tool-use preceded the development of large brains, or vice versa. Environmental explanations of cortical expansion avoid this problem. Two theories provide environmental explanations: 1) brain expansion was triggered by climatic variation (Ash and Gallup 2007) and 2) brain expansion was triggered by consumption of a shore-based diet (Cunnane and Crawford 2003). Both of these theories rely on fossil-record evidence linking brains of increasing size to particular geographical areas. Regardless of the trigger of brain expansion, the fossil record definitively indicates the influence of positive selection on brain size along the primate lineage leading to humans.

On a molecular level, the growth of the cerebral cortex is dependent on the unique pattern of cell division of neuronal progenitors. First, neuronal progenitor cells form at a narrow region around the telecephalic ventricle, where they then undergo symmetric cell division, giving rise to two daughter progenitor cells (Noctor et al. 2004). Each progenitor cell then divides asymmetrically, creating another progenitor cell and a neuron (Noctor et al. 2004). The sequence of events is strikingly similar across mammalian species. Identification of the genes responsible for regulating these specific cell division patterns provides another lens through which to examine the evolution of the cortex.

Research into the genetic causes of primary microcephaly in humans has identified two genes that are critical in ensuring the proper cell division of neuronal precursors. Those two genes are Microcephalin (MCPH1) and Abnormal spindle-like microcephaly associated (ASPM).

Comparative studies of the homologs of those two genes across species indicate that brain size has been under positive selection along the lineage leading to humans (Evans et al. 2004). However, research examining the coefficient of variance of brain size indicates that the brain is actually evolving more slowly than other organs of the body (Miller and Penke 2007). While this evidence could simply indicate that the evolution of brain size is operating under more stringent functional constraints, it could also be indicative of stabilizing selection (Miller and Penke 2007). The issue of whether brain size is currently under directional or stabilizing selection is thus still under debate.

Both fossil records and comparative genetic studies indicate that cortical size has been under the influence of positive selection over the long run. There is a discernable trend of increased encephalization along the primate lineage leading the humans. However, the rate of evolution of human brain size has slowed dramatically over time, leading to the hypothesis that the human brain is currently under stabilizing selection. I will discuss below the initial triggers of brain evolution and the reasons some scientists believe that the force governing the evolution of brain size has shifted from positive to stabilizing selection. I will also examine the hypothesis that different regions of the brain may currently be under the influence of different types of selection.

**Environmental triggers of brain expansion**

Examination of fossil evidence reveals a progressive increase in brain size along the mammalian lineage. This increase is particularly evident in the primate lineage leading to humans. Two theories suggest the influence of environmental factors: 1) Cunnane and Crawford's theory that consumption of a shore-based diet provided the trigger for brain

evolution and 2) Ash and Gallup's theory that climactic variation provided the trigger for brain evolution.

The theory that a shore-based diet provided the trigger for brain evolution is based on the observation that the brain makes exceptional nutritional demands on the body. In adult humans, the brain accounts for about 2.3% of total body weight yet uses about 23% of the body's daily energy (Holliday 1971). The energy demands of the brain are even more disproportionate in infants. At birth, the brain accounts for 11% of total body weight yet uses about 74% of the body's daily energy (Holliday 1971). Therefore, early hominids must have lived in an environment that would have afforded them the luxury of dedicating a high energy and nutrient supply to the brain. Cunnane and Crawford have proposed that fresh and salt water shorelines would have provided just this sort of nutrient-rich environment. According to their theory, hominids discovered and then exploited the abundant array of food available near bodies of water (lakeshores, estuaries, river deltas, marshes and seashores) of East and South Africa (Cunnane and Crawford 2003). Whether hominids lived on the shores of fresh- or salt-water bodies, mollusks, crustaceans, bird's eggs, spawning fish and frogs, and a variety of plant-life would have provided an energy-rich and readily accessible diet (Cunnane and Crawford 2003). Because this rich source of calories could have been acquired with relative ease, early hominids would have had the luxury of devoting more of their energy intake to brain development without jeopardizing their chances of survival.

Cunnane and Crawford argue that access to a nutrient rich diet might also have promoted brain development indirectly, through the development of other bodily processes. They illustrate this point by noting that, while the brains of humans and chimpanzees are approximately comparable in size immediately after birth, there is a substantial difference in the deposition of

fetal fat (Cunnane and Crawford 2003). At birth, body fat accounts for approximately 14% of human body weight, yet is virtually absent in chimps (Cunnane and Crawford 2003). This additional energy in fat stores provided human infants with the opportunity for brain expansion. The fat acts as expansion insurance in three ways: 1) it provides energy in the form of fatty acid triglycerides, 2) it provides the fatty acid precursors to ketone bodies required for normal brain development, and 3) it provides a supply of long-chain polyunsaturated fatty acids (Cunnane and Crawford 2003). The importance of fetal fat to brain development has been demonstrated through comparative studies of normal and pre-term infants. As most fetal fat deposition takes place in the final weeks of pregnancy, babies born 10 weeks early have about 10% of the fat of a normal term infant (Cunnane and Crawford 2003). While individuals who are born preterm generally develop mental capacities greater than those of chimpanzees, they often have smaller brains and slower rates of neurological development than normal term infants (Cunnane and Crawford 2003). It has thus been proposed that the shore-based diet led to the evolution of larger brains both directly, by providing energy necessary for brain expansion, and indirectly, by providing nutrient excess conducive to fat storage in the fetus. These hypotheses are supported by evidence from the fossil record linking early hominids to the shorelines of Lake Turkana, Kenya and Lake Victoria (Cunnane and Crawford 1993).

The main weakness of this study is that the data are purely correlational. While Cunnane and Crawford convincingly account for the presence of large-brained hominids near shorelines, they do not explicitly show that the first highly encephalized hominids were found there. To answer this objection, the study would need to include a comparative examination of fossilized remains from other areas from the same time period. This comparative study would need to demonstrate that larger skulls (reflecting larger brains) first appeared around shorelines. As the

study lacks such a comparative component, the possibility that hominids with bigger brains developed elsewhere and moved to the shorelines is not ruled out.

The authors of this study also place a great deal of emphasis on the idea that meat obtained through other sources could not have provided the trigger of brain expansion. This premise is not entirely convincing. Cunnane and Crawford make the point that, while consumption of prey would have met the energy demand necessary for brain development, obtaining this meat would have required a certain level of hunting skill (Cunnane and Crawford 2003). They argue that in order for hominids to hunt effectively, they would have needed tool-making and social skills that could only have developed as the result of brain expansion. As hominids did not have the natural bodily hunting implements of other predators like lions (e.g. sharp teeth, claws), I agree with the point that a certain level of tool-production and/or social coordination would have been necessary for effective hunting. However, in formulating their objection, Cunnane and Crawford ignore the likely availability of small game and carrion. Sophisticated hunting strategies would not have been necessary for obtaining either of those meat sources. Capture and consumption of small game would have been well within the range of capability for a Hominid with a level of encephalization equivalent to that of a chimp. The nutrient load of this meat could have also have served as the trigger for cortical evolution.

In addition, while the point about fetal fat deposition in human infants is unique and interesting, the authors fail to establish causation between the consumption of a shore-based diet and the fat deposition process. While it is highly possible that consumption of the nutrient-rich diet found along shore-lines provided conditions allowing for the unique development of fetal fat deposition mechanisms, the authors do not offer any concrete evidence to prove this point. Fossil records do not confirm (or deny) the presence of fat infants. While genetic studies could

demonstrate that the evolution of fetal fat deposition mechanisms preceded or coincided with increased encephalization, these were not performed. The idea that the unique pattern of human fetal fat deposition could have provided a trigger for brain evolution is deserving of further research.

A different theory proposing an environmental trigger of brain expansion posits that climactic variation and cooler temperatures in general provided the catalyst for increased encephalization (Ash and Gallup 2007). According to this "environmental variability hypothesis," inconsistency in environmental settings throughout the Pleistocene era may have favored adaptations that allowed for behavioral plasticity as a means of promoting survival (Ash and Gallup 2007). Increased brain size and the associated complex cognitive processes would have allowed for the development of a wide variety of adaptive behaviors. This increased array of adaptive behaviors would have led to an increase in the reproductive success of more encephalized Hominids in harsher environments.

Fossil records support this hypothesis by demonstrating that increases in cranial capacity in hominids were positively correlated with fluctuating extremes of environment (Ash and Gallup 2007). Oxygen isotope records and variations in sea-surface temperature (SST) were used as indices of past climate for the Pliocene and Lower Pleistocene time periods (Ash and Gallup 2007). Oxygen isotope measurements are valuable because they provide a representation of global glacial ice volume and temperature change. According to SST and oxygen isotope data, seasonal variation was particularly marked in mid to high latitudes, with temperature serving as the dominant climate variable (as opposed to humidity differences, etc.) (Ash and Gallup 2003). To address the idea that environmental variation might have been related to brain expansion, climatic variation was defined as the standard deviation of the climatic parameter (either SST or

oxygen isotope measurements) for the 200,000 years prior to the age of each cranium (Ash and Gallup 2003). Thus, a cranium aged 1.0 Ma was considered a product of the environment of the site of discovery 200,000 years prior. A study of 109 crania revealed that, the greater the distance between the excavation site and the equator, the greater the size of the skull (Ash and Gallup 2007). The geographical location of the fossil crania as measured by degrees latitude ultimately accounted for over 22% of the variance in absolute cranial capacity (Ash and Gallup 2007). Changes in SST and oxygen isotope values as a function time were also correlated with increases in cranial capacity (Ash and Gallup 2007). A graphical representation of this trend can be seen below in Figure 1.

**Fig. 1** Skull size as a function of mean values of oxygen isotope measurements taken at 100,000-year intervals

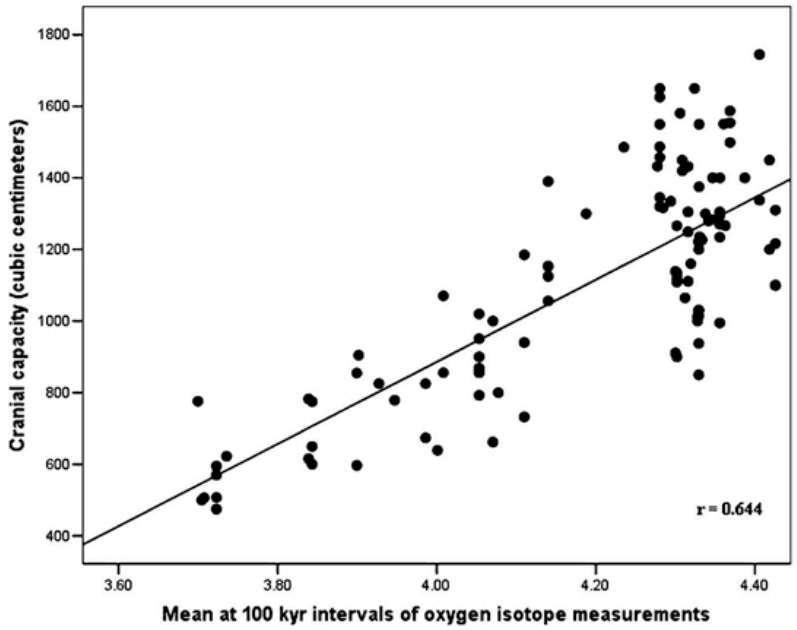


Figure source: Ash, J. and G. Gallup. "Paleoclimatic Variation and Brain Expansion during Human Evolution." Human Nature 2007 **18**: 109-124.

Small sample size is one major problem of this study. Given that the authors were attempting to establish a relationship between cranial size and climatic variability across both time and geographical space, the selection of 109 crania does not seem sufficient. Also, similar

to the objection I raised to the shore-based diet theory of brain expansion, I would argue that trends demonstrated in this study are again purely correlational. While it could be the case that climatic variability triggered brain expansion, we cannot rule out the possibility that hominids with greater cranial capacity preferred to settle in areas offering greater climatic variability. Locations with greater climatic variability could have offered advantages such as reduced resource competition to those organisms able to cope with the harsher standards of living. These advantages could account for the movement of hominids with increased cranial capacity to regions progressively distanced from the equator.

While the original trigger of increased hominid encephalization remains unclear, the fossil record does convincingly demonstrate that hominid brains grew larger with time. Gaining a proper understanding of the dynamics of this expansion is only possible through the examination of the unique cell biological properties of neuronal precursor cells.

**Cell biological processes underlying cortical expansion**

Two main features distinguish expansion of the cerebral cortex from expansion of other areas of the brain: 1) the increase in size of the cortex is caused by an increase in cell number rather than cell size and 2) the expansion of the cortex is lateral rather than radial; that is, surface area increases more than thickness (Fish et al. 2008). These unique patterns of expansion are the direct result of the particular cell biology of neural progenitor cells. Understanding the evolution of these cell biological properties is thus critical to understanding the evolution of cortical expansion.

Four specific cell biological processes are responsible for increases in neuronal cell number rather than cell size in the cerebral cortex. Three of those processes are involved in the division of apical neuronal progenitor cells of the ventricular area of the brain: 1) the

pseudostratification of the progenitor layer, 2) loss of mitotic-spindle rotation in neuronal progenitor cells, and 3) maintenance of symmetric progenitor divisions (Fish et al. 2008). The fourth process involves the division of the basal progenitor cells. In primates, the division of basal progenitors is radial and polarized, causing those cells to retain more epithelial characteristics than their apical counterparts. (Fish et al. 2008). Research by Fish's team indicates that evolution of the lack of spindle rotation in apical neuronal progenitor cells was the first critical step in the development and expansion of the cerebral cortex in mammals and later in the primate lineage.

Fish's team used genetic research conducted in *Drosophila Melanogaster* to demonstrate the effects of spindle rotation on the division of neuronal cells. In *D. Melanogaster*, expression of the gene Inscuteable produces protein products that mediate rotation of the mitotic spindle in neuronal progenitors, causing the cells to undergo asymmetric divisions along a horizontal cleavage plane (Fish et al. 2008). This manner of division is a hallmark of radial division, increasing the volume of the brain more dramatically than the surface area. Though also expressed in the neuronal cells of mammals, Inscuteable does not retain the same functionality (Fish et al. 2008). In mammals, Inscuteable does not mediate spindle rotation, meaning that fewer neuronal progenitors switch from modes of asymmetric division along a horizontal plane to modes of symmetric division along a vertical cleavage plane (Fish et al 2008). The increased number of divisions along the vertical plane leads to lateral expansion of the cortex. The benefits conferred by this sort of expansion may have led to the evolution of mechanisms to protect its function; that is, mechanisms to ensure the inhibition of rotation of the mitotic spindle and thus ensure preservation of symmetric division (Fish et al. 2008). The expression of abnormal spindle-like microcephaly associated protein (Aspm) is one example of a mechanism that may

have evolved to protect symmetric division of apical neural progenitor cells in the brains of mammals. Evidence of the influence of positive selection on Aspm expression along the lineage leading to hominids (detailed below) supports Fish's theory.

While Fish's theory seems well constructed, it could be that there are other mechanisms in place preventing the asymmetric division of neuronal precursors. Fish's theory could thus be strengthened by an experimental demonstration of the effects of forced spindle rotation in the apical neuronal progenitor cells of mammals. If Fish's theory is correct, forced spindle rotation should result in a switch in the cleavage plane, causing apical progenitors to divide in an asymmetric rather than symmetric manner. This difference should result in a cerebral cortex of reduced surface area. This experiment could be carried out by forcing the expression of the Drosophila Inscuteable gene in the neural progenitor cells of mice.

Research on the genetic determinants of diseases resulting in dramatically reduced brain size has identified several candidate genes that play an important role in determining cortical expansion. Protein products of these genes have functions that include, but are not limited to, regulation of spindle rotation.

**Evolution of microcephaly-associated genes**

An abundance of research has been put into identifying the genetic determinants of autosomal recessive primary microcephaly (MCPH). Though the basic architecture of their brains remains the same, individuals with MCPH have dramatically smaller cerebral cortexes (Bond et al. 2005). MCPH patients retain normal motor function, but display reduced cognitive capacity (Bond et al. 2005). By determining what 'goes wrong' in the brains of MCPH patients, researchers have gained insight into some of the causes of cortical expansion. The disease phenotype appears to be caused by altered division of neuronal progenitor cells, resulting in

fewer numbers of functional neurons. By identifying the genes mutated in MCPH patients, researchers have identified several candidate genes playing a role in neuronal progenitor cell division. By analyzing the homologs of these genes across species, researchers have been able to determine whether brain size has been under positive selection.

Mutations at six loci (MCPH1 – MCPH6) have been reported to cause clinically indistinguishable manifestations of the MCPH disorder (Bond et al. 2005). Thus far, researchers have determined that two of the genes commonly mutated in MCPH patients have undergone positive selection throughout primate evolution (Evans et al. 2004). These genes are microcephalin (MCPH1) and ASPM, which codes for the production of abnormal spindle-like microcephaly-associated protein (Evans et al. 2004).

MCPH1 codes for proteins responsible for DNA repair during the DNA replication processes in the S phase of the cell cycle (Evans et al. 2004). When MCPH1 is mutated, these repair proteins are not expressed and the cell fails to proceed through the cell cycle, arresting in G1 (Evans et al. 2004). Expression of this gene is most prominent within regions of active neurogenesis in the developing forebrain, demonstrating its importance in cortical expansion (Evans et al. 2004). It thus seems probable that this gene was under the influence of positive selection in highly encephalized animals. Construction of a phylogenetic tree based on MCPH1 reveals a trend of accelerated evolution along the primate lineage leading to modern humans (Evans et al 2004). The coding sequences of homologs of the MCPH1 gene were analyzed in a selection of species representative of key steps of the evolution of primates (Lemur, Squirrel monkey, Colobus monkey, Gibbon, Orangutan, Gorilla, Chimpanzee and human). The rate of gene evolution was determined by calculating the ratio of non-synonymous nucleotide substitutions (Ka) to synonymous nucleotide substitutions (Ks) between homologs (Evans et al.

2004). A ratio of Ka/Ks greater than one is taken as evidence of adaptive evolution (Evans et. al 2004). Figure 2 below shows the evolution of MCPH1 within primates, indicating the Ka/Ks ratio of each branch of the phylogenetic tree. Figure 3 shows the evolution of MCPH1 in other, non-primate taxa.

**Fig. 2** Evolution of MCPH1 within primates

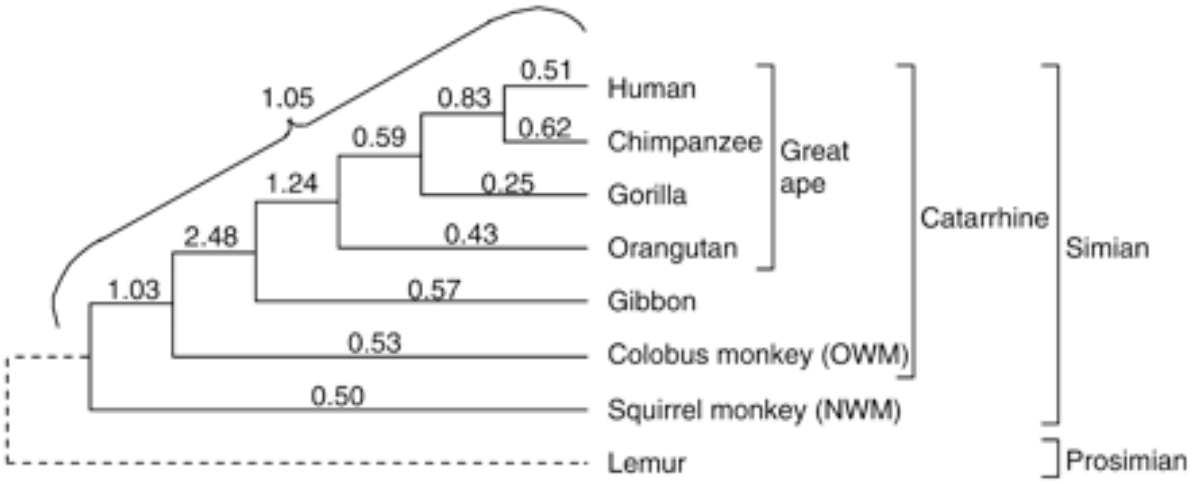


Figure Source: Evans, P.D., et al. "Reconstructing the evolutionary history of *microcephalin*, a gene controlling human brain size." Human Molecular Genetics 2004 **13(11):** 1139-1145.

**Fig. 3** Evolution of MCPH1 in other mammalian taxa

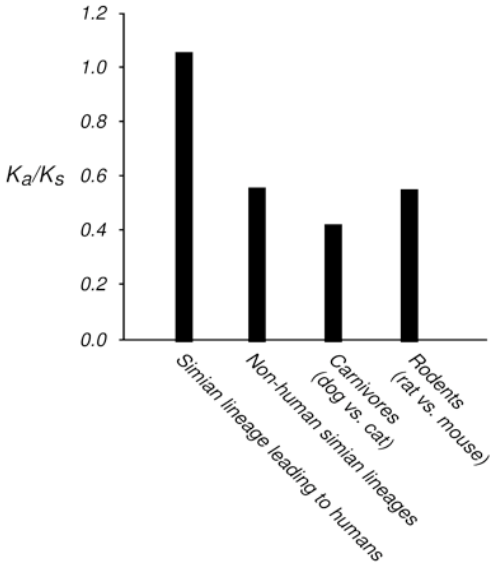


Figure Source: Evans, P.D., et al. "Reconstructing the evolutionary history of *microcephalin*, a gene controlling human brain size." Human Molecular Genetics 2004 **13(11):** 1139-1145.

As Figure 3 indicates, the Ka/Ks ratio is much higher along the simian lineage leading to humans than in other mammalian lineages. This finding indicates that positive selection has been acting on MCPH1 throughout the simian lineage leading to humans (Evans et al 2004). However, the authors of the study fail to discuss the fact that the evolution of MCPH1 has been slowing within the primate lineage leading to humans. As Figure 2 demonstrates, the Ka/Ks ratio has actually been falling along the simian lineage – at 0.51, the final branch of the phylogenetic tree marking the divergence of humans from chimpanzees has the lowest ratio. This trend seems to indicate that the evolutionary rate of MCPH1 has actually been slowing over time, perhaps due to the influence of stabilizing selection.

Like MCPH1, ASPM plays an important role in regulating the division of neuronal progenitor cells. In mammals, the protein products of ASPM localize to the poles of the mitotic spindle (Fish et al 2006). ASPM expression is necessary for maintaining the orientation of the mitotic spindle axis after the onset of anaphase, thereby ensuring symmetric cell division (Fish et al 2006). This maintenance of symmetric cell division promotes the lateral expansion of the cortex. ASPM is most highly expressed in the brain at sites of cerebral cortical neurogenesis, confirming its importance in the process of cortical expansion (Evans et al. 2004). The evolutionary rate of ASPM was analyzed by the same method used to analyze MCPH1. The rate of evolution of ASPM within primates is shown below in Figure 4.

**Fig. 4** Evolution of ASPM within primates

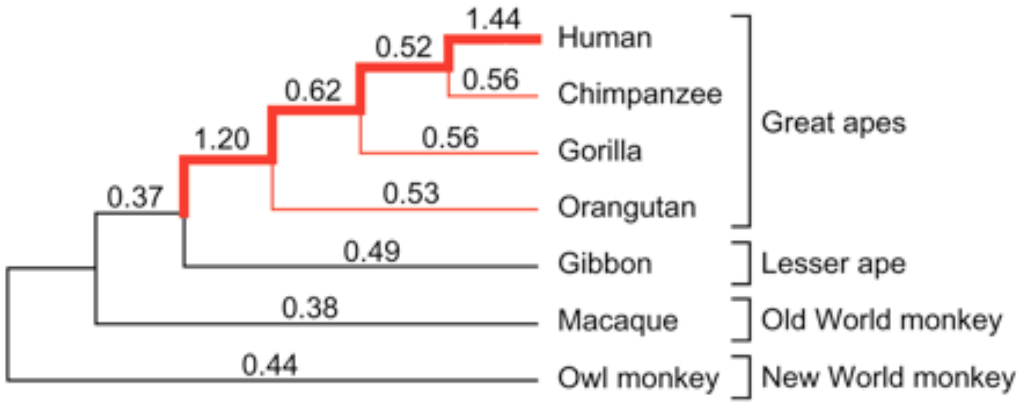


Figure source: Evans, P.D., et al. "Adaptive evolution of ASPM, a major determinant of cerebral cortical size in humans." Human Molecular Genetics 2004 **13(5)**: 489-494.

**Fig. 5** Evolution of ASPM in other mammalian taxa

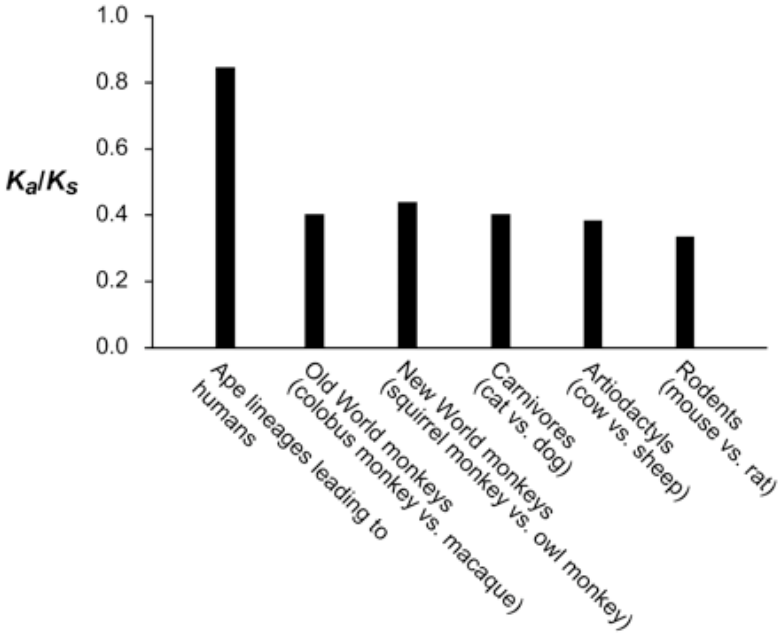


Figure source: Evans, P.D., et al. "Adaptive evolution of ASPM, a major determinant of cerebral cortical size in humans." Human Molecular Genetics 2004 **13(5)**: 489-494.

In noting that both ASPM and MCPH1 have been under positive selection along the primate lineage, Evans seems to grossly oversimplify his own findings. While Evans' conclusions are accurate, he fails to address the fact that the evolutionary rate of MCPH1 has been slowing along the lineage leading to modern humans, while the evolutionary rate of ASPM

has been accelerating. As Figures 2 and 4 show, the Ka/Ks ratio of MCPH1 is 0.51 along the branch of the phylogenetic tree leading to humans, while the Ka/Ks ratio of ASPM along the same branch is 1.44. This data seems to indicate that MCPH1 is coming under stabilizing selection, while selection pressures on ASPM are increasing. The differences in evolutionary rates could be due to the fact that MCPH1 and ASPM affect cell division in different ways.

It is important to note that, while MCPH1 and ASPM are highly expressed in cortical structures, their expression is not limited to the brain (Ponting and Jackson 2005). While MCPH1 and ASPM are both critically important to ensuring that neuronal progenitor cells divide properly, their functions may not be equally important to the proper division of other cell types. Specifically, as MCPH1 codes for proteins involved in DNA repair during chromosomal replication, its expression would be critical in cells of any bodily tissue. ASPM, however, is responsible for regulating the cleavage plane, ensuring that neuronal cells first divide in a symmetric rather than asymmetric manner. While the manner of cell division is important in the context of neuronal progenitors, it may not be as important for cells of other tissues. Thus, less stringent selective constraints may act on ASPM, leaving it freer to evolve than MCPH1. It is also possible that the function of ASPM is redundant, thus giving the gene more freedom to evolve under positive selection. As I mentioned in the previous section about cell biological processes underlying the division of neuronal cells, symmetric division is the natural state of neuronal progenitor cells. While ASPM ensures symmetric division, this is not to say that all neuronal precursor cells would divide asymmetrically in its absence. ASPM seems to function as a kind of insurance mechanism, ensuring that neuronal progenitor cells divide in a manner conducive to lateral expansion. However, since this function is not entirely necessary, it would not be subject to evolutionary constraints.

Taken together, the evolutionary rate data indicates that MCPH1 evolved before ASPM. Though MCPH1 may have come under stabilizing selection, this does not necessarily indicate that evolutionary forces no longer favor expansion of the human brain. In summary, examination of the evolution of microceophaly associated genes convincingly indicates that brain size has been under positive selection along the mammalian lineage leading to humans. However, whether human brain size is currently under positive or stabilizing selection remains unclear.

**Coefficients of variance**

Examination of the coefficient of additive genetic variance of human brain size indicates that the human brain is currently under stabilizing selection (Miller and Penke 2006). The coefficient of additive genetic variance (CVA) is a measure of the variation of a trait attributable to genetics, rather than environment. The CVA of a trait is a dimensionless quantity that is computed as a trait's coefficient of phenotypic variation multiplied by the square root of its narrow-sense heritability (Miller and Penke 2006). Evolutionary biologists have discovered that traits directly related to reproductive fitness and traits under directional selection tend to have high CVA values (Miller and Penke 2006). Meanwhile, strong stabilizing selection, which favors strict canalization and mutation-resistance during development, drives the CVA towards 0 (Miller and Penke 2006). CVAs can thus be used as indices of recent selection. The CVAs of a variety of traits are shown in Table 1 below.

**Table 1**: Compilation of CVAs in a variety of traits

| Trait | CVA |
|---|---|
| Great tit: badge size (known to be under directional selection) | 9.9 |
| Bollworm moth: Pheromone blend (known to be under stabilizing selection) | 2.8 |
| Human eye: central corneal thickness | 8.09 |
| Human brain volume | 7.8 |
| Human lung volume | 10.2 |
| Human knee cartilage volume | 20.5 |
| Human thyroid gland volume | 24.7 |
| Human heart: left ventricle volume | 31.7 |
| Human penis volume | 37.0 |
| Human breast volume | 61.5 |

Data compiled from: Miller, G. and L. Penke. "The evolution of human intelligence and the coefficient of additive genetic variance in human brain size." Intelligence 2007 35: 97-114.

The CVA of brain volume in modern humans was calculated using measures of brain volume taken from MRI studies. At 7.8, the CVA of brain volume is comparable to that of sexual ornaments known to be under directional selection and significantly greater than that of sexual traits under stabilizing selection (Miller and Penke 2006). However, the CVA of brain volume is significantly lower than the CVA of any other volumetrically measured human trait, indicating that brain volume may be under stabilizing, rather than directional, selection (Miller and Penke 2006).

The observed stabilizing selection could be attributed to the anatomical constraint imposed by female pelvic size (Miller and Penke 2006). The human brain is the largest bone-encased structure that must fit through the mother's birth canal during childbirth. Prior to the (relatively recent) development of Cesarean sections, babies with excessively large heads would frequently die or cause the death of their mothers during childbirth. Thus, the chances of babies with larger-than-average brains surviving to pass on the genes responsible for the enlargement would be slim. Such an obstetric constraint could have imposed much of the stabilizing selection on brain size, dramatically reducing the CVA of brain volume (Miller and Penke 2006).

While it is possible that the modern human brain is under stabilizing selection, I would like to posit three counterarguments to the conclusions of this study. First, Miller and Penke could simply have chosen poor standards of comparison, making the CVA of brain volume seem comparatively low. Miller and Penke note that many organs, including hearts and lungs have the ability to grow and shrink over time as a result of physiological demands (Miller and Penke 2006). Thus, the higher CVA values for these organ volumes may reflect temporary differences in organ use rather than stable variation in baseline size. Meanwhile, penis and breast size can vary tremendously without functional consequence. The fact that the CVAs of these sexual organs are several orders of magnitude higher than that of brain volume does not necessarily mean that brain volume is under stabilizing selection – it simply indicates that brain growth is more constrained.

Second, a low CVA could be a reflection of a high level of genetic redundancy in the brain. Given the particular importance of brain function, it is probable that an array of genes codes for the development of any given necessary structure or process. Such redundancy would guard against the adverse effects of a mutation in any given brain-development related gene. In such a system, certain genes important to brain expansion (such as MCPH1 or ASPM) could be under strong positive selection while genes regulating other features of development could be under stabilizing selection. If the genes under stabilizing selection were more prominent, this would explain the low CVA of the brain. Third, I propose that the CVA of the surface area of the cerebral cortex might provide a more accurate representation of the role of selection on brain evolution than the CVA of brain volume.

As I have discussed in previous sections of this paper, the development of the cerebral cortex in humans is primarily attained through lateral growth. The ‘wrinkled’ appearance of the

cerebral cortex is the result of efficient packing of a large sheet of brain material into a relatively small space. While the volume of the brain may be restricted by the obstetric constraints mentioned above, it is possible that the surface area of the cerebral cortex is much more widely variable. As the cerebral cortex plays a key role in memory, attention, perceptual awareness, thought, language and consciousness, it is likely that the surface area of the cerebral cortex is much more highly correlated with intelligence than brain volume. The theory that brain volume is under stabilizing selection usually seems to conflict with the idea that there should be positive selection for increased intelligence (Miller and Penke 2006). An established link between intelligence and cortical size would provide a way around this conundrum.

Research conducted by Tuller, Kupiec, and Ruppin may refute the hypothesis that positive selection plays a greater role on evolution of the cerebral cortex. Research by Tuller's team indicates that genes highly expressed in the brain have significantly lower evolutionary rates (ERs) than genes highly expressed in somatic tissues (Tuller et al. 2008). Within the brain, genes highly expressed in cortical regions have lower ERs than genes highly expressed in subcortical regions (Tuller et al. 2008). The fact that genes expressed in the cortex are more highly conserved than genes expressed in subcortical regions could account for some, but not all of the difference between evolutionary rates (Tuller et al. 2008). Higher mean levels of gene expression in cortical rather than subcortical regions can at least partially explain this difference in conservation (Tuller et al. 2008).

It is important to note that the evolutionary rates calculated in Tuller's research are averages of all highly expressed genes in a given area. The lower ER of the cerebral cortex could thus be the result of genes with widely varying ERs – some highly expressed cortical genes could have extremely low ERs, balancing the effect of genes like ASPM that are under positive

selection. Thus, the lower ER of the cortex does not necessarily mean that some processes involved with cortical development are not under positive selection. It could also be the case that the genes responsible for mediating the manner of division of neuronal progenitors in the cortex are not particularly highly expressed (relative to other genes) and are not included in Tuller's calculations. As Tuller did not provide a list of genes analyzed, it is impossible to determine whether ASPM was included in his analysis. While some genes of the cortex must be highly constrained to support Tuller's findings, his results do not necessarily preclude cases of positive evolution on certain developmental processes of the cortex.

**Concluding remarks**

Evidence from the fossil record and studies of evolutionary rates generally show that brain size was under positive selection through the first several branches of the primate lineage, but has come under stabilizing selection during Hominid evolution. The only piece of evidence directly conflating this trend shows evidence of positive selection on the ASPM gene along this most recent branch of the phylogenetic tree leading to humans. As ASPM is implicated in the division of neuronal precursors leading to lateral expansion of the cerebral cortex, this indicates that the surface area of the cortex may still be under positive selection, even if overall brain size is not. The cerebral cortex is essential for memory, thought, awareness and language acquisition – fundamental hallmarks of human intelligence. If it is the case that the size of the cerebral cortex is still under positive selection, this would support the common hypothesis that human intelligence is still under positive selection. It would be interesting for future research to determine the CVA of a linear measurement of the cerebral cortex and examine the possible link between cortical surface area and intelligence. A glance through recent literature indicates that mathematical models are being developed to 'flatten' the cortex, determining a measure of its

linear size based on MRI data. These mathematical models could be highly instructive in solving the question of whether intelligence is still evolving.

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