The new work from Shan and colleagues demonstrates the expanding reach of molecular dynamics simulations and sets the stage for future investigations of EGFR regulation, its oncogenic activation, and inhibitor binding properties. For example, it will be interesting to know what effect inclusion of Mg^{2+} and ATP in the molecular dynamics calculations has on the observed conformational rearrangements. Additionally, the present simulations do not reveal the transition to the inactive conformation targeted by lapatinib. Though it may be no small matter to extend the simulation timescale sufficiently to observe this transition, it will be of interest to computationally characterize the relative stability of the active, disordered, and fully inactive states.

This study also provides a few testable hypotheses that may move the field forward. For instance, if different activating mutations stabilize the active state via distinct mechanisms, one might expect that, in combination, they would yield higher levels of activity, further shifting the equilibrium toward dimerization. Finally, the prediction that phosphorylation of Tyr845 in the EGFR activation loop activates the kinase and stabilizes the EGFR dimer may motivate the field to re-examine the role of this phosphorylation event in EGFR signaling.

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Sibling Rivalry among Paralogs Promotes Evolution of the Human Brain

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DOI 10.1016/j.cell.2012.04.020

Geneticists have long sought to identify the genetic changes that made us human, but pinpointing the functionally relevant changes has been challenging. Two papers in this issue suggest that partial duplication of *SRGAP2*, producing an incomplete protein that antagonizes the original, contributed to human brain evolution.

Humans differ from the other great apes in many ways, one of the more obvious being our larger, more complex brains. These human-specific characteristics have evolved in the last 6–7 million years since we split from our common ancestor with chimpanzees and bonobos. We can catalog the phenotypic differences between humans and other great apes, and in some cases, we can determine when they evolved, using evidence in the fossil record. Brain size increased throughout this period, although unevenly (Figure 1A and 1B), but fossil details of internal brain structure are sparse. In a complementary way, we can catalog the genetic differences between humans and chimpanzees from their genome sequences (Chimpanzee Sequencing and Analysis Consortium, 2005) and identify which differences arose on the human lineage by comparison with an outgroup—a species external to the chimpanzee-human branch, such as gorilla (Scally et al., 2012). But there are around 20 million genetic changes that are specific to humans, most of which probably have no functional impact whatsoever. How do we pick out the few functionally relevant changes and link them to their phenotypic consequences? Two papers in this issue of *Cell* now show one way that this can be accomplished

(Charrier et al., 2012; Dennis et al., 2012). The authors characterize a series of partial duplications of the single ancestral *SRGAP2* gene. They make a strong case for the duplicates leading to a higher density of spines on dendritic cells in the brain and contributing to the neotenous development characteristic of humans.

How do you sift through 20 million genetic differences? A good starting point is the subset of changes that have major effects on protein-coding genes, which includes duplications and deletions. A previous systematic survey of such copy number changes in great apes had identified 140 events that are specific to the human lineage (Fortna et al., 2004), including several that are implicated in neuronal function. These should be enriched for functionally important changes. Among them was *SRGAP2*, which was shown in mice to regulate neuronal migration and morphology (Guerrier et al., 2009). *SRGAP2* was therefore an excellent candidate for more detailed investigation of the link between a genetic change and evolution of the human brain.

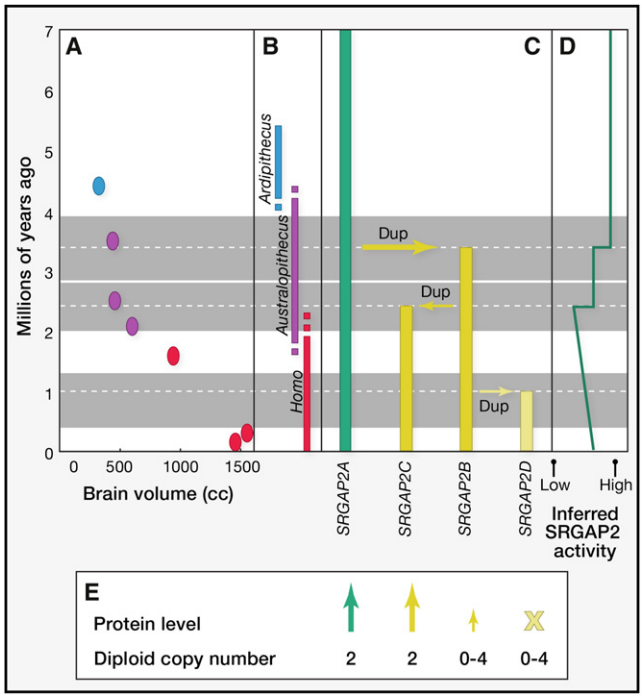

Figure 1. Evolutionary Context of *SRGAP2* Duplications on the Human Lineage

(A–D) The vertical axis shows evolutionary time from the present (0, bottom) to 7 million years ago (top). Horizontal dotted lines represent times of *SRGAP2* duplications with their uncertainty indicated by gray shading.

(A) Brain volume estimates of fossils and living humans, colored according to genus.

(B) Timescales of genera thought to include human ancestors.

(C) Sequence of duplication events of *SRGAP2* copies.

(D) Inferred SRGAP2 activity as a consequence of duplication of antagonistic paralogs and the decay of *SRGAP2B*.

(E) Levels of protein (schematic) and copy number of paralogs in modern humans.

Investigations of gene duplicates (i.e., paralogs) can face substantial obstacles. Copies recently duplicated remain similar in sequence—almost as similar as alleles—and often confuse genome assemblies; indeed, the *SRGAP2* gene family was grossly misassembled in the human reference sequence. Now, Dennis et al. (2012) present an approach to characterize the paralogs that should be widely applicable: use DNA from a haploid source, a complete hydatidiform mole (the product of fertilization of an enucleated oocyte by a single sperm) in which there are no allelic variants to confound assembly, and sequence large-insert clones. This allows the authors to identify four copies: the parental *SRGAP2A* and its three duplicates *SRGAP2B–D*, and also to infer the order of the duplication events, *A* > *B* > *C* > *D*, with *C* and *D* independently derived from *B* (Figure 1C). These findings are fully consistent with the less detailed conclusions of the accompanying study (Charrier et al., 2012). Furthermore, comparisons of the *SRGAP2* sequences suggest that the duplication events occurred ~3.4, ~2.4, and ~1.0 million years ago. The first event duplicated only 9 of the 22 exons, truncating SRGAP2 in its F-BAR domain; therefore, all of the other duplicated copies are also truncated, with key functional consequences.

The duplicates are all expressed, and, given their similarity, sorting out their specific roles is challenging. The first simplification comes because there is an additional deletion within *SRGAP2D*, removing exons 2 and 3; this, together with its absence from some individuals in the general population, suggests that it is unlikely to play any important role (Figure 1E). Interest thus focuses on *SRGAP2B* and *C*, which are extremely similar in sequence. Their expression patterns are also similar, but again there are simplifying factors: the level of *SRGAP2B* transcripts is low, and it is also absent from some normal individuals (Figure 1E). Thus, the main player is SRGAP2C, and its interaction with SRGAP2A. This cannot have always been true during the evolution of humans; later in this Preview, we will discuss the more important role that SRGAP2B must have played earlier in evolutionary history.

Previous work on the mouse ortholog of SRGAP2A (srGAP2 or Srgap2) had shown that it induced filipodia formation in the developing cortex through its F-BAR domain; in addition, decreasing the levels of SRGAP2A reduced axonal and dendritic branching and increased the rate of neuronal migration (Guerrier et al., 2009). Now, Charrier and colleagues (2012) use mouse and cultured cell models to understand the functional consequences of the human-specific *SRGAP2* duplications. The authors further characterize the phenotypes resulting from *Srgap2* knockdown or knockout and compare them with the effects of *SRGAP2C* expression. *Srgap2* knockdown leads to neurons with increased densities of immature-looking dendritic spines in juveniles. Knockout mice are viable even as homozygotes, retaining ~10% of *Srgap2* expression, and show continued growth of spine heads during development, with the result that spine head size in adults is close to wild-type, but spines are more numerous and necks are longer. SRGAP2C can dimerize with SRGAP2A through its truncated F-BAR domain and decrease SRGAP2A activity. Strikingly, the simple conclusion is that *SRGAP2C* expression closely mimics the *Srgap2* knockdown and

knockout phenotypes in almost all of the characteristics examined. In summary, the functional studies suggest that SRGAP2C, by reducing SRGAP2A activity, contributes to human-like features, including extended brain development—neoteny—and cell structure in the neocortex.

In humans, the phenotypes associated with natural loss-of-function or duplication variants of *SRGAP2A* and *C* are of great interest. Particularly relevant is a balanced translocation disrupting one copy of *SRGAP2A* in a 5-year-old girl with symptoms including intellectual disability and seizures (Saitsu et al., 2011). Loss or gain specific to *SRGAP2C* has not yet been reported, but Dennis and colleagues find large duplications affecting numerous genes, including *SRGAP2C*—predicted to increase SRGAP2A antagonism—in both one control and three patients with intellectual disability and/or autism spectrum disorder. Further surveys of human variants and their detailed phenotypes, particularly *SRGAP2C* deletions, should be highly informative.

These conclusions have several implications for our thinking about human evolution. The duplications would have had immediate and perhaps substantial phenotypic effects (Figure 1D). *SRGAP2B*, the progenitor of *SRGAP2C*, must have been an active antagonist at the time of its duplication 3.4 million years ago, and SRGAP2 activity would have reached a minimum after the *SRGAP2C* duplication 2.4 million years ago (Figure 1D). These duplications would have occurred in *Australopithecus* species (Figures 1B and 1C). Did they have consequences for gross brain anatomy that might be recognized in rare fossil endocasts, e.g., Dart (1925) (mouse models might be informative here), and did they contribute to the development and behavior of these species documented by paleontologists? Intriguingly, the use of recognizable stone tools began about 2.5 million years ago (Jobling et al., 2004), and brain size started to increase soon after (Figure 1A), but it is difficult to test for a direct link. Neoteny has long been recognized as a human characteristic (Bufill et al., 2011), and now we can begin to understand its genetic and developmental basis.

ACKNOWLEDGMENTS

Our work is supported by The Wellcome Trust (098051).

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