the authors also show that familial clustering can occur between some cancers at *different* sites: a pattern which indicates that cancer might be considered a broad phenotype with shared genetic factors that are not site-specific.

The study of familial disease risks for relatives outside the nuclear family is difficult because of the difficulties both in identifying distant familial connections and in confirming cancer diagnoses in distant relatives. The ICR contains almost complete records of all cancer cases diagnosed in Iceland since 1955, 95% of which are histologically verified, and the deCODE genealogy database includes information on all 288 000 currently living Icelanders and 400 000 deceased individuals – a large proportion of those who have ever lived on the island. The linkage of these two databases has provided a unique data source for investigating the risks of developing cancer in both close and more distant relatives of cancer cases.

A statistically significantly increased risk to first- and second-degree relatives was seen for 20 of the 27 most prevalent sites. Nonsignificant increases were seen for the other seven sites, but in all seven the risk estimates were based on fewer than 800 cases. The magnitude of the first-degree relative risks are consistently around two-fold for all the common cancers. These results are broadly in line with the results of other large population-based studies.[3,4] Of greater interest, perhaps, was the observation of significantly increased risks in third- to fifth-degree relatives at 14 sites including all of the eight commonest cancers. In most cases, there was a decline in risk from first- to fifth-degree relatives as would be predicted for monogenic disorders or for an additive polygenic model.

In addition to site-specific risks, risks between pairs of sites were estimated. In total, 17 cancer sites were involved in 20 significant pairs. Stomach and prostate cancer appeared most frequently in the pairs followed by colon, ovarian and cervical cancer. However, the power to link rare cancers to other cancer sites might have been lacking. High-risk alleles of genes known to be involved in heritable syndromes might partly explain some of these connections, but clusters were also identified between cancer sites for close and distant relatives that do not correspond to known cancer syndromes. One explanation for this finding would be an interaction between common environmental risk factors such as tobacco smoke or diet and genetic factors, so that the same gene–environment interaction could induce different cancers. One notable risk cluster was that of hormone-related cancers. This pattern indicates that genetic susceptibility factors might directly influence hormonal metabolism to induce several different cancers. Cancers with common developmental origins also tended to occur in risk clusters, which might reflect the presence of risk alleles that regulate embryonic development. A broader interpretation of these data, and one that has more profound implications, is that cancer can be considered a broad phenotype with shared genetic factors across cancer sites. Considering cancer in this way has some important practical implications: in particular, it should be possible to combine different cancer sites to increase the power of linkage and case–control studies■

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Evolutionary Genetics

The human brain – adaptation at many levels

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What makes a human brain bigger and more 'complex' than other primate brains, and how did these changes evolve? Steve Dorus *et al*,[1] in their study recently published in *Cell*, show, by comparing rates of protein evolution between primates and rodents, that there is an accelerated rate of evolution of some nervous system genes in humans. This study reaches some exciting conclusions and highlights some of the promises and pitfalls of comparative genomic analyses that are being used to shed light on the genetic legacy of human evolution.

As the metric of adaptive protein evolution, the authors used the K_a/K_s ratio,[2] which compares the number of nonsynonymous substitutions (K_a; changes that affect the amino-acid sequence) to the number of synonymous substitutions (K_s; changes that do not affect the amino-acid sequence) between two DNA sequences. In a departure from previous studies,[3] the authors chose to calculate K_a/K_s in primates through

comparisons of human and rhesus macaque sequence. This strategy avoids the problems that the high degree of sequence similarity between humans and chimpanzees – the species most often used in such comparisons – generally poses: high stochastic uncertainty and reduced statistical power to detect evolutionary adaptations. In order to calculate K_a/K_s in rodents, the authors chose two species separated by roughly comparable evolutionary distance: the rat and the mouse. They obtained orthologous sequences from all these species for a select group of 214 genes, which are said to play important roles in the nervous system.

Although none of the genes examined showed strong evidence of positive selection in either rodent or primate lineages (ie none had $K_a/K_s>1$), the average rate of protein evolution across all genes was significantly higher for the primate comparison than the rodent comparison. This disparity was absent in a comparison of 95 'housekeeping' genes, but was even more pronounced for the subset of genes placed in the nervous system development group; whereas nervous system genes placed in the routine physiological 'maintenance' group were less likely to differ between rodent and primate lineages.

To determine whether the acceleration identified in primates occurred on the human lineage, Dorus and colleagues compared K_a/K_s between human and rhesus macaque, using the squirrel monkey as a common reference group, and then between human and chimpanzee, using rhesus macaque as a common reference group. In both cases, the subset of genes showing the highest levels of acceleration in the primate lineage also revealed a significantly higher average rate of protein evolution in the human lineage. The authors argue that these genes are likely to represent targets of adaptive evolution during recent human evolutionary history, noting that many are known to be involved in the control of brain size and behavior. In addition to providing a new data set, this study offers a novel perspective on primate evolution. However, given the significance and breadth of the authors' conclusions, several aspects of the study and its conclusions warrant further inspection.

First, since the number of genes examined represents only a fraction of all genes expressed in the nervous system, it is critical to understand their unstated selection criteria in order to rule out any ascertainment bias. Second, the authors' choice of a control group of genes plays a pivotal role in their analysis. It is not surprising that the nervous system genes selected differed from the control group, given that housekeeping genes are extremely conserved and yield an average K_a/K_s that is both small and relatively constant across phylogeny.[4] An equivalent study that compared nervous system genes with other tissue-enriched genes (eg kidney or liver), might provide stronger evidence for adaptive evolution in primate nervous system genes. Third, fundamental characteristics of primates and rodents such as mutation rate, life cycle, and effective population size throughout history (eg human population bottlenecks) obscure the interpretation of differences in K_a/K_s between the two groups. Fourth, there is no *a priori* reason to discount the possibility that relaxation of constraint might actually precede adaptive evolution (see Hayakawa *et al*[5]). Thus, to clarify these initial findings, the authors' approach should be extended to surveys of more genes representing more tissues and more species.

Comparative analyses of amino-acid sequences also measure only one area of genomic divergence. Selection also operates in other important dimensions, such as changes that affect the regulation of gene expression. Several recent studies have used microarrays to measure levels of gene expression in brain tissue from humans, chimpanzees, and other primates, and have provided evidence for hundreds of significant differences in the human brain (reviewed in Preuss *et al*[6]). Also, evidence of positive selection acting on a gene implicated in nervous system development does not guarantee that the nucleic acid changes observed in the genome will necessarily affect the function of the protein during early development, when one considers the multiplicity of roles that might exist for a given protein across different tissues and stages. Combining such analyses with anatomical studies will aid in their interpretation by providing a cellular and stage-specific context. Undoubtedly, both alterations in protein structure and in the regulation of gene expression worked in concert with the environment to sculpt the human brain into its modern form.

This raises a fundamental question: mechanistically, what were the primary drivers of evolutionary change? Was there, in fact, a rapid accumulation of functionally significant single-base substitutions affecting the primary sequences of hundreds or even thousands of proteins? Or did genomic remodeling take place on a larger scale, perhaps affecting multiple genes simultaneously, as has recently been described in humans[7]? In the first detailed comparison of an entire chimpanzee chromosome (22) to its human counterpart (21), nearly 68 000 insertions and deletions were identified over a genomic span of 33.3 megabases,[8] or about 1% of the human genome. Somehow, all of these differences need to be considered if we are to succeed in reconstructing our evolutionary past.

Ultimately, however, understanding the evolution of the human brain will depend on more than sequence data. Genetic adaptations that sequence comparisons identify must be recast in phenotypic terms. In the case of the brain, this will require detailed functional analyses that span molecular, cellular, and systems neurobiology. Simple explanations of human uniqueness predicated on general notions of increased brain size and complexity are no longer sufficient. So what are the relevant human brain phenotypes to which genetic adaptations might pertain? Many aspects of human cognition are likely to emerge from the intrinsic properties of a system that allows for increased plasticity and efficient learning of advantageous new cognitive or behavioral strategies, as in the case of reading and writing.[5] If plasticity is the key, how many changes at the genome level were necessary to build this feature into the human brain? The answer to this question is of fundamental importance, and although early efforts in a field often raise more questions than they answer, such studies provide a crucial gauge of our progress.

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