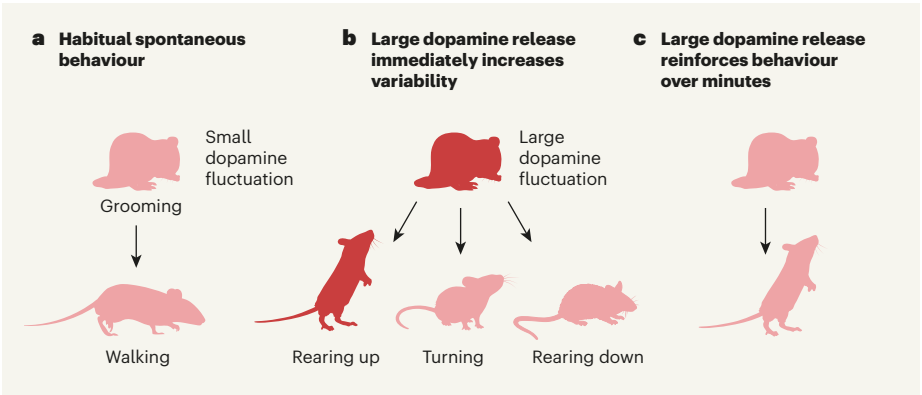

Figure 1 | How dopamine curates routine behaviour. a, Markowitz *et al.*[1] report that, when a mouse is engaged in a sequence of spontaneous behaviour, switches between elements of activity called syllables (such as grooming and walking) are accompanied by small fluctuations in the release of the neurotransmitter dopamine (indicated by pink colouring). **b**, A large dopamine fluctuation (red) induces immediate variability in subsequent syllables. **c**, The large fluctuation also reinforces behaviour, making it more likely that a syllable that coincides with a large dopamine release (here, grooming) will be used again. Presumably, whichever of the subsequent variable syllables also coincides with a large dopamine release (here, rearing up) becomes reinforced too, forming a new routine behaviour, although this was not explicitly tested.

better food source? Various theoretical solutions for resolving this trade-off have been proposed[8,9], but they typically deal with the quantity (how much) and quality (how) of exploration. In the context of spontaneous behaviour, Markowitz and colleagues' findings — with random exploratory behaviour taking place immediately after dopamine release — might offer a surprising answer for the dynamics (when) of exploration. Whether this phenomenon occurs in the context of reward learning is an open question; however, it stands to reason that, after a reward, a sated animal can afford the risk of venturing away from the safety of known actions.

The dual effect observed by Markowitz *et al.* is consistent with what we know about the physiological changes that dopamine brings about in the DLS, and in the striatum in general. Like other neuromodulators and neurotransmitters, dopamine acts on DLS neurons by binding to specialized receptor proteins. Dopamine binding has two effects. It causes a slow cascade of events resulting in the long-term plasticity of active neuronal circuits[10,11], perhaps underlying the reinforcement of spontaneous behaviour. And it leads to an immediate increase in the excitability of the subgroup of DLS neurons that promotes actions, together with a decrease in the excitability of the subgroup that inhibits actions[12–14], perhaps underlying the increased variability seen by the authors. This is a prime example of how larger-scale complex processes can be reduced to mechanisms that are grounded in basic cellular physiology.

The current study provides valuable insights into the moulding of continuous everyday behaviours, and highlights previously unknown functions of dopamine. A next step will be to determine what triggers the dopamine fluctuations. Dopamine release might be controlled locally within the DLS[15], or might be regulated by the nucleus-housing cell bodies of dopamine neurons, which are located in the midbrain. Because the DLS is only one target of midbrain dopamine, the latter scenario could indicate that changes in dopamine levels are also communicated to other brain areas, with further effects on behaviour. The fluctuations might be 'noise' that hijacks the existing reinforcement-learning circuitry to ensure a wide repertoire of natural behaviours, or could be somehow related to the actions themselves.

Finally, it will be interesting to determine whether neuronal activity in the DLS itself influences dopamine release, creating a feedback loop. Clearly, the authors' findings are a promising sign that further discoveries await.

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Genetics

Fast-evolving DNA drives human brain development

Eucharist Kun & Vagheesh M. Narasimhan

Regions of the human genome that evolved rapidly after the separation between hominins and chimpanzees have now been charted. They contain genomic elements that are unique to humans and are linked to neurodevelopment and disease.

What are the genetic changes that separate humans from chimpanzees? The discovery that there is little difference between these species in terms of protein-coding DNA sequences has led to the hypothesis that the genomic changes responsible for human-specific traits are mainly evident in the non-protein-coding region of the genome[1]. Writing in *Cell*, Mangan *et al.*[2] report that the most rapidly evolving of these non-coding regions are related to human-specific neurodevelopment and disease. The work provides insights into how we differ from our great-ape ancestors.

So far, most studies of human-specific evolution have examined either coding DNA or non-coding regions that are highly evolutionarily conserved in all vertebrates, but mutated at a faster rate in humans than in other species[3]. These genetic sequences, named human accelerated regions (HARs), mostly reflect existing regulatory elements in DNA that have evolved more rapidly in humans[4,5]. However, highly conserved regions make up only about 5% of the human genome[4].

Mangan *et al.* took a broader view, looking at the entire genome, which consists largely of non-conserved regions, to identify sequences that have undergone human-specific evolution. They aligned all great-ape and human genome sequences to computationally infer the genome of the last common ancestor of humans and chimpanzees. By comparing the modern human genome with that of the human–chimpanzee ancestor, they identified rapidly diverging sequences, which they dub human ancestor quickly evolved regions (HAQERs).

The authors identified 1,581 HAQERs, which were heavily mutated in humans compared with other species. They found that HAQERs had undergone more genetic changes in a given timeframe than had HARs, making them the fastest-evolved regions in the human genome. Furthermore, there were only 6 places in which HAQERs overlapped with one of the 2,733 previously identified HARs, suggesting that the regions identified in this study were previously unknown.

What mechanisms underlie the rapid divergence of HAQERs? Mangan *et al.* found that these regions are uniquely associated with both higher mutation rates than other genomic regions and stronger positive selection for certain genetic variants. HAQER sequences are also highly similar in different hominins (humans, Neanderthals and Denisovans), but not in chimpanzees. This finding suggests that HAQERs underwent rapid evolutionary selection after the human–chimpanzee split, but were evolutionarily constrained (that is, subject to strict limits on selection) within hominins (Fig. 1).

Next, the authors showed that HAQERs are most common in genomic regions involved in the regulation of gene expression in two regions of the body — the brain and gastrointestinal tract. These findings are in line with evidence from the fossil record showing that brain expansion and gut reduction occurred after the separation of hominins from chimpanzees.

Regulatory DNA sequences called enhancers do not encode proteins, but instead increase the expression of target genes. Mangan *et al.* used a modified form of an assay known as STARR-seq to measure enhancer activity in HAQERs associated with brain development. They found higher levels of enhancer activity in hominin HAQERs than in the same regions in chimpanzees or the inferred human–chimpanzee ancestor. In fact, the non-hominin sequences exhibited almost no enhancer activity, suggesting that HAQERs are regulatory elements that gained function for the first time in the hominin lineage owing to mutation and selection, rather than having evolved from a previously existing regulatory element as is the case in HARs.

Gene duplication is a key evolutionary process associated with the emergence of new genetic functions[6]. Mangan and colleagues observed groups of HAQERs close to human-specific duplicates of two genes, *FOXD4* and *NBPF*, which are associated with neuronal differentiation and increased brain size, respectively. The researchers suggest that rapid changes in these HAQER regions, followed by gene duplication, led to increases in expression of the duplicated genes. They suggest that this combination of regulatory innovation and gene duplication could have contributed to how human-specific genomic regions evolved so rapidly.

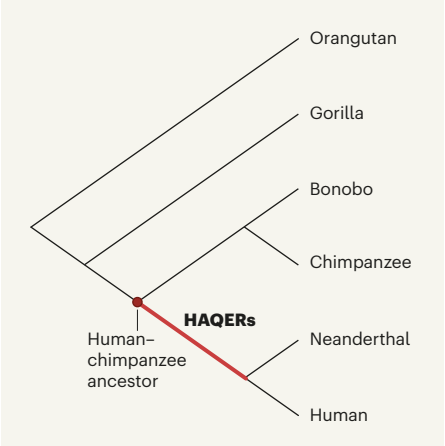

Figure 1 | Identifying human ancestor quickly evolved regions (HAQERs). Mangan *et al.*[2] compared the genomes of great apes and hominins, as well as an inferred sequence for a common ancestor of humans and chimpanzees. This enabled them to identify regions called HAQERs, which evolved rapidly before the split that led to the evolution of Neanderthals and humans. HAQERs contain newly evolved sequences that promote the expression of genes involved in human neurodevelopment and disease (not shown).

Many neuropsychiatric diseases, including schizophrenia, are specific to humans[7]. Mangan *et al.* found that variants in HAQERs are linked to a range of conditions, including high blood pressure, a type of nerve cancer called neuroblastoma, bipolar disorder and schizophrenia. The authors propose that these associations are mainly due to the elevated mutation rates in HAQERs, and suggest that, although rapid evolution yielded traits that are beneficial to humans, it also led to susceptibility to human-specific diseases.

Mangan and colleagues' exciting analyses reveal regions of the genome that can be studied to improve our understanding of the divergence of humans from our close relatives. Going forward, these newly identified regions are likely to be connected to human-specific functions, or possibly revealed as drug targets for diseases known to affect only humans.

The group's work is also timely because many complete, high-quality genomes for myriad vertebrate species are being generated through efforts such as the Vertebrate Genome Project[8]. The approaches used in the current study can be applied to a range of species to identify other fast-evolving regions and pave the way for new kinds of comparative genomic analysis. Moreover, ongoing advances in genomics will enable the study of HAQERs themselves to be expanded to regions that had previously been difficult to sequence, such as highly repetitive elements, and even perhaps genomic regions surrounding the chromosome-fusion event that led to humans having only 46 chromosomes instead of 48, as do other primates — a major genomic difference between us and our closest relatives.

Analyses of human genomic evolution often focus on the brain. However, from a morphological perspective, most information about human evolution is available only from the skeleton — usually the sole tissue preserved in the hominin fossil record. This fossil record provides insights into the evolution of bipedalism, which might have occurred before brain development, including changes to the shape of the pelvis and the lengths of the limbs[9]. The part that HAQERs play in the evolution of our ability to walk on two legs will be an interesting topic for future research.

Finally, ancient DNA from skeletons could highlight intermediary genomic and temporal points in human evolution. Last year, researchers obtained DNA from two-million-year-old samples[10]. As technology improves, it might be possible to obtain genetic data from extinct hominins, such as *Homo naledi*, *Homo erectus* and *Australopithecus*, that split off from the modern human lineage after chimpanzees but before Neanderthals. Information from such genomes would further clarify the types of genomic change that occurred in our evolutionary history, and help us to understand the process of HAQER divergence.

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