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Spotlight

A Molecular Investigation of Human Self-Domestication

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The question of whether human beings are like domesticated animals in their behavior has been simultaneously intriguing, hard to define precisely, and seemingly resistant to any kind of scientific test. A recent paper by Zanella *et al.* reports a molecular-genetic approach to it and provides a provisional 'yes'.

The idea that human beings resemble domesticated animals, in their relative docility and general lack of aggression toward one another, has had a long history (Box 1). How does one evaluate it scientifically, however? Part of the problem is definitional since domestication lacks a generally accepted meaning. Correspondingly, there has been an absence of agreed criteria for what constitute it. Another difficulty is imagining how domestication might take place in the absence of an obvious domesticating agent, as would be the case for humans. A possible solution for the latter is the idea that an animal species might develop lower aggressiveness and greater sociality through its own evolution via self-domestication [1–3]. The bonobo, also called the pygmy chimpanzee, provides an example [1]. Might humans similarly be self-domesticated animals?

A recent paper provides a possible molecular and genetic entrée to the problem. It starts from the premise that there is a domestication syndrome; a suite of morphological and physiological traits that accompany domestication [1,4]; a phenomenon first described by Charles Darwin [5]. The particular set of traits is taxon specific, but the striking observation is how often particular traits recur within the group of 26 domesticated species of mammals [6,7]. Wilkins *et al.* [4] noted that these traits share developmental origins in the early embryo involving neural crest cells; many, and perhaps, all of the traits of the domestication syndrome are consistent with their resulting from small decreases of neural crest cells at relevant sites, relative to nondomesticated forbears. This is now termed the neural crest domestication syndrome (NCDS) hypothesis. This suggests one can reframe the question about human self-domestication as: are there are any signs of a domestication syndrome, based in neural crest cell biology, in humans?

The new paper by Testa and Boeckx and their colleagues investigates the matter from this angle [8] Its starting point is Williams–Beuren syndrome (WBS) or Williams syndrome; a condition resulting from a hemizygous 1.8 Mb deletion on chromosome 7, the region 7q.ll.23. It features many psychological changes, including cognitive deficits but high verbal ability and enhanced sociality, as well as alterations to the facial bones leading to 'elfin' features. Since the bones of the face derive from neural crest cells, there is a prima facie case that WBS involves some partial dysfunction of neural crest cells, a neurocristopathy, leading to smaller facial bones. WBS is thus a neuropsychiatric condition and a neurocristopathy, possessing elements of both domestication (low aggressiveness and high sociality) and the domestication syndrome (reduction of facial bones). The focus of the work was the gene *BAZ1B*; one of the genes removed by the WBS deletion. *BAZ1B* is known to be necessary for neural crest cell migration; an essential element in development of neural crest-based traits. *BAZ1B* is a well-characterized chromatin-remodeling gene, hence a transcriptional regulatory gene. The first major part of the work dealt with the regulatory properties of the gene and its role in the basic biology of forming the facial bones in the embryo. The authors first derived neural crest stem cells from individuals with both WBS and others possessing the converse condition; a duplication of the WBS region. They also had cells from one patient that bore a partial WBS deletion sparing the *BAZ1B* gene, thus possessing the normal (double) dosage of the gene. They then tested the cell-migratory abilities of these different cell lines with three different dosages of *BAZ1B* gene (single, double, and triple), and their gene regulatory abilities for hundreds of genes. The findings were striking: not only was there a clear relationship between *BAZ1B* dosage and the speed and ability of the cells to migrate (in an *in vitro* wound-healing test), mimicking likely neural crest cell behavior, but comparable dosage-dependence in gene regulatory ability, at the chromatin-transcriptional level, for the expected genes involved in craniofacial bone morphogenesis, including key known neural crest cell genes

Box 1. The Long History of Ideas about Human Domestication

The first speculation linking human nature to domestication was made by Aristotle (cited in [3]). Two millennia later, the idea was taken up by Jean-Jacques Rousseau (cited in [9]). The modern history of the idea, however, traces back to Johann Blumenbach, an early commentator on human races, in the early 19th century and then to Charles Darwin in his magnum opus on human evolution in 1871 [10]. Darwin, however, ultimately rejected the notion on the grounds that there could have been no domesticator for humans, in the way that humans have domesticated animals. The major discussions of the putative resemblances, however, took place later, in the first half of the 20th century, and involved principally German scholars. The various commentators, however, were divided as to whether the putative resemblances between domesticated animals and humans was a positive feature, reflecting sociality and cooperativity, or a negative one, reflecting weakness and degeneracy in modern humans, compared to presumed more courageous forebears (reviewed in [9]). Although much of this earlier work had a negative character and eugenic speculations, current work emphasizes solving the genetic and biological roots of human self-domestication and casts human nature in a more positive light.

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known to be required for this process, such as *TFAPA2* and *ZEB2*. In effect, *BAZ1B* is a master regulator of gene expression for genes required for the bones of the face and acts in a dose-sensitive fashion.

The second part supplies the possible connection to human self-domestication. Comparing the DNA sequences in and around the *BAZ1B* gene from the genomes of contemporary anatomically modern humans (AMHs), with those of archaic hominins, Neanderthals, and Denisovians, the authors found fixed mutations in the regulatory regions of the gene from AMHs, but not the archaics. These mutations are almost certainly mild loss-of-function mutations, which would cause slight reductions in the amounts of the gene's expression and, ultimately, in the bones of the face. This is significant because AMHs have slightly reduced facial bones compared with the archaic hominims; this parallels the domestication syndrome in other mammals. Thus, this work ties neural crest cell molecular biology to the expected phenotype one expects for the human developmental biology that might go along with domestication.

Altogether, Zanella *et al.* have produced an elegant and convincing piece of work that strengthens both the NCDS as a mechanism underlying domestication and the case that humans are a domesticated, indeed a self-domesticated, species. Many questions about these issues remain, of course, in particular concerning the links between the molecular biology of the genes involved and the neurobiological foundations of the social behaviors in Williams syndrome. Nevertheless, the work described in Zanella *et al.* is a model for exploring the possible connections between complex behavioral states and their developmental origins and evolutionary correlates. Not least, such studies should deepen our understanding of what domestication is.

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Forum

Genetic Variation across Phenotypic Severity of Autism

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It is still unclear how genetic factors of autism spectrum disorder (ASD) are implicated in the significant clinical heterogeneity ranging from intellectual disability (ID) to high-functioning profiles. Here, evidence from recent genetic studies encompassing common and rare variants are combined to suggest a genetic model that may explain the broad gradient of phenotypic severity observed in ASD.

ASD represents one of the most prevalent disorders in childhood [1]. Family and twin studies that started more than 20 years ago have pointed clearly to a strong genetic component underlying this disorder [1].

Hundreds of studies have thus far substantially increased our knowledge of the genetics of ASD implicating several genes in the disorder. Only a decade ago we were debating which genetic hypothesis – 'common disease, common variants' or 'common disease, rare variant' – was better at modelling the genetics of autism. Currently, we know that both hypotheses are partially correct.

Many different classes of variants shape ASD genetic liability [1,2], including: (i) common risk alleles from SNPs; (ii) mutations that are rare in the general population or single nucleotide variants (SNVs); (iii) loss/gain of genetic material defined as copy number variants (CNVs); (iv) and *de novo* variants (SNVs or CNVs). Genetic studies conducted to date converge on a genetic model in which both multiple common variants of small effect size and rare variants with moderate or higher penetrance are implicated in the genetic landscape of ASD (Figure 1). Besides the genetic changes identified thus far, DNA methylation and other epigenetic alterations are also likely to contribute to autism. However, DNA methylation studies have generally been performed in small samples [1] and currently no conclusions can be drawn about the extent of epigenetic heritability in ASD.

Notwithstanding the recent advances in unravelling the genetic causes of autism, we acknowledge that the real genetic architecture is far more complex than previously thought. We have journeyed