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**Searching for the genetic foundations of animal domestication: hypotheses and genomics data**

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The start of the scientific study of “domestication” of animals (and plants) began with this man...

Charles Darwin, 1809-1882
The fruit of his researches was this two volume work, whose full title is *Variation in Animals and Plants under Domestication*, first published in 1868.
The outcome of this massive work?

A theory of heredity that convinced almost no one and was subject to extensive criticism from many who had supported Darwin’s theory of evolution. Unbeknownst to Darwin, a much better theory had been produced and published two years earlier, by an amateur breeder, the Augustinian friar Gregor Mendel, but this work would not be known for decades more, about 18 years after Darwin and Mendel had died. (They both died in the year 1882).

The real accomplishment of Darwin’s work on heredity, though this was not appreciated at the time, was the discovery that breeding for domesticated varieties, of both animals and plants, tends to produce certain common changes, characteristic of the domesticated state. This set of traits associated with domestication has been termed the “domestication syndrome”. All domesticated animal species must have been selected initially for docility and tameness but then a fair number of other traits developed as a result. This discovery was Darwin’s big contribution to the subject.
What precisely is the set of traits that comprise the “domestication syndrome“?

Hence, the “domestication syndrome”, while a real phenomenon is a general condition rather than a tight or narrowly defined set of traits invariably associated with domestication. It is, in effect, a family or related conditions.

Nevertheless, that similar phenotypic changes appear again and again in different domesticated species suggests that certain shared developmental processes are affected amongst the different domesticated species but not necessarily that the same genes have been affected.

So, we now come to the explicit genetic question:

What are the gene sets affected in domestication, what are the “domestication genes“?
“Domestication genes“: before trying to identify them, two broad possibilities, illustrated for three domesticated animal species, appear.

Wholly independent sets

Sets with some important overlaps
A key question that then arises from these considerations:

If you strip away the genetic changes associated with selection for specific traits in different domesticated animals (for example, milk production in cows, egg size in chickens, speed in racing horses) is there a core set of common genetic changes specific to the phenomenon of domestication itself?
Four hypotheses about the genetic foundations of domestication

1. The “null“ hypothesis: that each case of domestication is different and that the initiating genes are quite different in each case

2. The “Genetic Regulatory Network“ (GRN) hypothesis: that the properties altered in domestication are all underlain by a large GRN and that upstream mutations in this genetic network cause the “domestication syndrome“

   (Dmitri Belyaev and Lyudmilla Trut)

3. The “thyroid hormone hypothesis“ (THH): that domestication involves neotenous (slowed down) development and that alterations in thyroid hormone metabolism are chiefly responsible

   (Susan Crockford, 2002)

4. The “neural crest cell hypothesis“ (NCCH) hypothesis: that the domestication syndrome is underlain by alterations in (mild) deficits of neural crest cells for the different traits altered in the DS.

   (Adam Wilkins, Richard Wrangham, Tecumseh Fitch, 2014)
Some fundamental facts about thyroid metabolism and development
Neural crest cells and their differentiated derivatives
With respect to some of the specific major “phenes” of the “domestication syndrome”
The basic genomic predictions of the two hypotheses:

1. The THH hypothesis predicts that mutations in genes of thyroid metabolism will be found in genomic studies of (all) domesticated animals

2. The NCCH hypothesis predicts that mutations in “neural crest cell genes” will be found in genomic studies of all domesticated animals
<table>
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<tr>
<th>Animal type</th>
<th>Study</th>
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<td>KIT, MC1R</td>
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<td>PCDHA1, PCDHD4, ARID3B, DCC, PLEKHH1, KIT</td>
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<td>FGF13, WNT9b, WNT3, ZIC3, AXIN2, AXIN11, SMO, NOL11, SNX19, PRKCA, WF1KKN1</td>
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Over-all conclusion: There is only weak support for the THH but much stronger support for the NCCH

Two important caveats:

1. There is a key thyroid hormone metabolism gene, the TSHR gene, in chickens which is implicated in several aspects of the DS in chickens.

2. More generally, there is the possibility that the screens that have been done are missing a lot of the key genetic changes, those in crucial cis-regulatory sequences, so called conserved non-coding elements (CNE).
Perhaps the biggest question in animal domestication, however, concerns “tameness” itself:

What are the genetic and neurological foundations of tameness?
Selection for Tameness

Reduced neural crest input ("mild neurocristopathy")

- Reduction in adrenals & sympathetic ganglia
  - Reduced stress,
  - Reduced fear of humans,
  - Learning: "humans OK".

- White patches (melanocytes)
  - Floppy ears (chondrocytes)
  - Reduced muzzles, & jaws (osteoblasts)
  - Reduced teeth (odontoblasts)

- Reduced forebrain size
  - Potential indirect side-effect of reduced neural crest input

Direct developmental results of reduced neural crest input

Selected Traits

Unselected By-Products
Let us look at the second possibility: that tameness is a secondary effect from neural crest cell influences on brain development.

1. cranial neural crest cells (CNCC)
2. Fgf8
3. promotes telencephalon and diencephalon development (by suppressing apoptosis)
   (The “Sophie Creuzet” effect)

Two questions: Are these effects quantitative? Can mild CNCC depletion cause mild forebrain reduction?

And, if so, is the neural circuitry governing tameness affected by such reductions?
The question of tameness relates to the possibility or, at least, question of “self-domestication” in a few key species. Have these species “tamed” themselves?

wolves to dogs

Chimp-like ape to bonobos

modern humans??

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From the Abstract:

“…We provide evidence that structural variants in GTF21 and GTF21RD1, genes previously implicated in the behavioral phenotype of patients with WBS and contained within the WBS locus, contribute to extreme sociability in dogs. This finding suggests that there are commonalities in the genetic architecture of WBS and canine tameness and that directional selection (for tameness) may have allowed for rapid behavioral divergence of dogs and wolves, facilitating coexistence with humans.”
Hypersociable dogs and the “elite” (super-friendly) domesticated foxes: the same genetic changes involved?
Where do we go from here? A few questions to think about:

1. Do mutations in particular neural crest cell genes tend to correlate with specific “phenes” of the domestication syndrome?

2. How many, and which, key genetic changes in cis-regulatory regions are we missing?

3. Is there a quantitative relationship between degree of tameness and the number of genes mutated that contribute to it? Or are there simply key genes that confer this phenotype, with different mutations in those genes giving different degrees of effect?

4. Whatever the genetic sources of tameness, why do some mammalian species seem resistant to domestication?

5. How do the brain size effects play into domestication? Are there genuine exceptions to the general rule of brain size reduction during domestication or will more careful measurements reveal that it always accompanies domestication?

6. Does animal domestication by humans shed any light on the possibility of human “self-domestication”? 
My two partners in developing the neural crest domestication syndrome hypothesis (NCCH):

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