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Correlated behavioural selection responses during animal domestication

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Abstract

This essay is an overview of the domestication process, with focus on correlated selection responses and genetic mechanisms. Domesticated animals share many common traits and could have emerged as a correlated response to increased tameness, or lower fear of humans. The chicken is an important model in domestication research as it is available in its wild ancestral form and is used for comparative studies as well as selection experiments. QTL studies have been used to find genetic regions that are correlated to quantitative traits. Finding genes that control behaviour is in most cases difficult because of the nature of behaviours and because behaviours are often controlled by several genes of small effects. Determining the genetic mechanisms behind animal domestication will not only shed light on this evolutionary process but can also be used to improve animal welfare in a time where increased production rate is highly valued.

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1. Animal domestication

Humans have used animals for food production and companionship among other things for a long time. According to archaeological findings, the dog was the first species to be domesticated at least 12,000-14,000 years ago (Leonard et al. 2002; Pennisi 2002). Evidence from genetic studies even suggest that dogs may have been domesticated already about 32,000 years ago (Thalmann et al. 2013; Wang et al. 2013). Many other animal species, predominantly livestock like chickens and sheep, have been domesticated since then. Some of the domesticated animals today were initially used for other purposes. Chickens, which are predominantly used for food production today, were initially used for ceremonial purposes and cockfighting (Keeling 2002).

A commonly cited definition of domestication is the one by Price (1984). Domestication can be defined as the process by which animals become adapted to humans and the environment that they provide (Price 1984). His definition includes effects that are brought about by experience, e.g. docile behaviour towards humans due to habituation. Jensen and Wright (2014) write that "Domestication is the process whereby populations of animals change genetically and phenotypically in response to the selection pressure associated with a life under human supervision." This definition clarifies that domestication is an evolutionary process in which the effects develop continuously over generations, just like speciation. Similar to the problem of defining animal species, we have a difficulty in determining when an animal is truly domesticated. Domesticated animals are characterised by a coherent set of phenotypical characteristics that is termed the domesticated phenotype (Price 1999).

During domestication, the genome of a species changes over generations leading to adaptation of the animal to the captive environment provided by humans. The mechanisms behind these changes are not yet completely understood. Genetic linkage and pleiotropy have been proposed as possible mechanisms and they will be discussed further in this essay.

1.1 The domesticated phenotype

The domesticated phenotype is a set of phenotypic traits that are common to all domesticated species. Compared to their wild ancestors, domesticated animals often have piebald markings, they tolerate or even seek human companionship, have altered body proportions (e.g. shortened snout, elongated or shortened legs) and reproduce outside of the normal breeding season. Reduced body size seems to be one of the most common traits associated with domestication (Clutton-Brock 1999). There are however exceptions to this observation, e.g. in animals that have been selected for production traits such as increased growth of muscle and high egg yield or large size for other reasons, e.g. in dogs and horses.

Figure 1. An example of two different domesticated species, both shown here with floppy ears and an altered coat colour compared to their wild ancestors.

Earlier sexual maturity is a common trait in domesticated animals. Compared to wolves, dogs become sexually mature already a year earlier (Boitani and Ciucci 1995). In chickens, we see that the domesticated White Leghorn female starts laying eggs when it is around 20 weeks old, whereas the red junglefowl starts about five weeks later (Schütz et al. 2002). Other physiological changes have also occurred in domesticated animals. A common change in domesticated species is a smaller relative brain size. This has been reported in e.g. mink (Kruska 1996), pigeons (Rehkämper, Frahm, and Cnotka 2008) and sheep (Ebinger 1974), among others. Although many studies have found the same pattern, two different studies in rainbow trout found conflicting results. One population of fish had smaller brains as expected (Marchetti and Nevitt 2003) whereas another study found the opposite with domesticated fish having a larger brain (Campbell et al. 2015). Perhaps a more interesting observation is that separate parts of the brain seem to have changed in differing proportions in domesticated animals, e.g. guinea pigs Kruska (2014) and sheep Ebinger (1974).

Reduced sensitivity to stress is an important change in domesticated animals. One of the main regulators of the stress response is the hypothalamic pituitary adrenal (HPA) axis. A relaxation of the HPA-axis responsivity has been reported in rats (Albert et al. 2008), guinea pigs (Künzl and Sachser 1999) and silver foxes (Harri et al. 2003) among other domesticated species. Domesticated animals are also much less fearful of humans (Price 2002). The behavioural repertoire of domesticated species has generally not changed, but rather the frequencies of the behaviours due to changes in the thresholds for the behaviours(Price 1999). For example, the domesticated White Leghorn layer shows less contrafreeloading compared to the ancestral red junglefowl (Lindqvist and Jensen 2002) and there is an overall reduced level of activity, more relaxed social

structures as well as less explorative behaviour (Schütz and Jensen 2001). Feral dogs form social groups that can change form one day to the next both in size and composition, whereas wolves aggregate in stable social groups with close relatives (Boitani and Ciucci 1995).

Species that have been domesticated also share some key traits that make them susceptible to domestication. These traits are often termed as preadaptations to domestication and they help the animals cope with living in the captive environment. For example, the animals often have precocial young, promiscuous mating systems and eat an omnivorous diet (Price 1984). One of the most useful preadaptations to domestication is living in social groups with a hierarchy as this makes it possible for the human to substitute as the leader of the flock.

1.2 The captive environment

Compared to the environments in which the wild ancestors of our domesticated species come from, the captive environment is usually a lot different. We tend to keep animals in small spaces with a lot of other individuals because of space limitations. It can be difficult for an animal to escape from a dominant conspecific. An important change in practically all domesticated animals is that they are less sensitive to environmental change (Price 1999), but this does not mean that they are not affected by environmental change. Animals in the production industry are often moved during the different stages of rearing. This can include everything from moving to another pen, stable or even a completely different farm. Social hierarchies are challenged by such transitions since the constellation of the social group is likely to change. Red Junglefowl live in smaller groups with a harem structure (Collias and Collias 1996) but in commercial chicken housing the animals are commonly housed in groups of thousands of individuals. White Leghorns (selected for high egg production) less frequently engage in social interactions, as well as other energy demanding behaviours, compared to Red Junglefowl and Swedish Bantam (Schütz and Jensen 2001). It is quite possible that engaging less in social interactions is beneficial in an environment where the amount of conspecifics is larger than what an individual is capable of recognising. Flock size also affects the degree to which chickens exhibit behavioural synchrony, with synchrony decreasing with increasing numbers of birds in a group (Keeling, Newberry, and Estevez 2017).

Predation pressure is greatly reduced or even eliminated in the captive environment. With the removal of predators, traits and behaviours aimed at avoiding predation become less important. Humans can even favour traits that would be disadvantageous in the wild. For instance, coat colour variation is more abundant in domestic animals (Cieslak et al. 2011) and especially interesting is white colouration which is considered detrimental for wild animals that rely on inconspicuous coat colour for camouflage.

2. Genetic mechanisms in domestication

As previously mentioned, the genetic mechanisms underlying domestication are largely unknown. Previous research indicates that epigenetic modifications can

be inherited to the offspring. This mechanism of inheritance could be responsible for the of the observed fast changes in traits seen in domesticated animals. Lindqvist et al. (2007) found that the gene expression response to stress treatment was transmitted from parents to offspring in White Leghorn chickens. Gene expression and methylation patterns have also been found to be consistent in the brain between parents and offspring in chickens, showing that epigenetic variation is inherited in this species (Nätt et al. 2012).

On the premise that selection for tameness only would bring about correlated selection responses that resemble the domesticated phenotype, an experiment was started by Belyaev (1979) in 1959. The purpose of the study was to mimic early domestication using silver foxes, a species that had not been domesticated prior to that. It is known as the farm fox experiment and it is a classic example of correlated selection responses. Belyaev and his group selected silver foxes from a farm-bred population on one trait only, tameness. The test used for the selection was the glove test, where the response of a fox to an approaching human gloved hand was measured. For breeding, the foxes that showed the highest and lowest fearfulness were used to select two different lines of foxes. This procedure was followed for several generations.

Examples of traits that were developed in the selected foxes are floppy ears, loss of pigmentation and faster ontogenetic development (Trut, Oskina, and Kharlamova 2009). The changes are also common to the domestic dog. It is quite interesting considering that the only trait that was selected for was the level of tameness. Similar selection studies of fearfulness towards humans have been done on rats (Albert et al. 2009), mink (Malmkvist and Hansen 2002) and chickens (Agnvall et al. 2012). Rats selected for tame behaviour towards humans tolerate handling and touch whereas aggressive rats perform behaviours such as boxing, attack and screaming (Albert et al. 2008). Effects on physiology were also seen, where tame rats had larger kidneys, brains and spleens. Mink selected for lower fearfulness approach and start to eat novel food faster than fearful individuals (Malmkvist and Hansen 2002). They are also less fearful in other novel situations involving novel objects and environments. Like mink, chickens selected for lower levels of fearfulness towards humans are bolder in a novel object test (Agnvall et al. 2015).

Kukekova et al. (2011) found an association between tame and aggressive behaviour in foxes at a locus on the VVU12 chromosome. This region is orthologous to another found by vonHoldt et al. (2010) in dogs and wolves. For rats, two significant quantitative trait loci (QTL) for tameness have been found (Albert et al. 2009) that are not orthologous to the loci on fox VVU12 (Kukekova et al. 2011). The discovery of non-orthologous loci for tameness in foxes and rats shows that there are several possible pathways of evolution of tameness. Further research into this area in other species may reveal interesting results.

Pleiotropy is the main reason for correlated selection responses, although linkage can also be a transient cause (Falconer 1989). Pleiotropy is defined as the situation where two or more seemingly unrelated traits are controlled by a single locus (Stearns 2010). Correlated selection responses due to linkage are

especially common in crosses between divergent lines of animals, such as those used for QTL studies. Genes that are situated close to each other on the same chromosome have a higher probability of being inherited together compared to genes that are located far away from each other or even on a different chromosome. During meiosis, there is recombination where crossing-over of the chromosomes happens. In this recombination event, genes located closely together are likely to be inherited together. We use this to our advantage when performing analyses of possible QTLs.

2.1 QTL mapping

A Quantitative Trait Locus (QTL) is a locus that contains alleles that differentially affect the expression of a continuously distributed phenotypic trait. QTL-studies are useful in determining regions in the genome that are linked to certain phenotypic traits. The basic principle of QTL mapping involves a cross between two lines of individuals that are divergent in a trait. Breeding designs used for this differ, but a common one is an F2-intercross. The segregation of genetic markers can then be analysed through a statistical association between the markers and phenotypic traits. Traits affected by several genes can in this way be linked to specific areas on the chromosomes (Weller 2009). This is the first step in finding the actual genes or mutations that are responsible for a proportion of the variation in a trait.

Genetic markers (positions of sequence variation) such as single nucleotide polymorphisms (SNPs) and microsatellites are dispersed throughout the genome. These are used in QTL mapping (among other mapping techniques) to determine regions of possible QTL. The trait of interest is scored according to the frequency of which it appears associated to any of these markers. A high frequency of association is an indication of the marker being close to a gene of interest.

The simplest method of QTL mapping is single marker analysis. What is done here is a comparison of the behaviour of individuals with different marker genotypes. Statistical tests are used to determine if there is a difference in the phenotype between the marker genotypes for each marker location separately. The principle is the same for interval mapping, but instead of comparing each individual marker location we compare pair of adjacent markers. A problem with single marker analysis is that the estimation of QTL effects will be affected by the distance between the QTL and the marker. We will not be able to determine whether the QTL has a major effect and is located far from the marker or if the effect is minor with the QTL located close to the marker. For this reason, interval mapping is preferred over single marker analysis. However, single marker analysis is more flexible as it is easier to add covariates to the model. The issue with single marker analysis becomes smaller with an increasing density of markers.

As briefly mentioned earlier, two divergent lines or populations can be intercrossed to determine genomic regions that affect a trait. When it comes to domestic animals and the cases where there is an extant ancestor, this is very

useful (Andersson and Georges 2004). The difficulty of identifying genes that affect behavioural traits is that behaviours are generally not controlled by a single gene. The contribution of each gene can be small and there are environmental effects that need to be considered. To eliminate environmental effects on a trait in an experiment as much as possible, animals need to be housed in a standardised environment. Any differences in phenotype should then mainly be due to genetic effects. However, environmental effects can be unpredictable and a completely standardised environment is very difficult, probably even impossible, to create. To increase the statistical power of our analysis, we need to use many individuals, especially since the genes we are looking for usually have a small effect.

The ultimate goal of QTL mapping is to eventually pinpoint actual genes and mutations underlying a QTL. There are however several difficulties with doing that. Previous QTL- and genome-wide association studies (GWAS) show that single genes only account for a proportion of the variation in a quantitative trait, which lowers the resolution (Flint and Mackay 2009). In studies where actual genes have been identified, the effect size of the QTL has been very high compared to most QTL effect sizes (Flint et al. 2005). Effect size is the proportion of the trait variation that is attributable to a specific QTL. Environmental factors as well as other QTLs affect quantitative traits. So, the probability if detecting a gene or mutation that corresponds to phenotype in a quantitative trait is low. It is also difficult to pinpoint the exact location on a chromosome due to the number of markers and crossover events.

Difficulties aside, there are several methods for going from a QTL-region down to a specific gene. To increase the mapping resolution, an advanced intercross line (AIL) can be made (Darvasi and Soller 1995). Instead of two generations of intercrossing of two diverging strains, several more generations are performed in an AIL. This increases the recombination frequency, which therefore also increases the resolution of the genetic map and gives a better estimate of the QTL. When a trait is correlated to a marker, one can assume that a gene responsible for the trait is located close to the marker. The region can be sequenced and compared to already known sequenced genes. In this way, a candidate gene can be found that corresponds to the investigated trait. After this, we need to further determine the function of the gene on the phenotype to be able to determine if the gene regulates it or not. A popular method in mouse genetics is gene knock-out. The function of a gene of interest is knocked out to determine which effect it has on the phenotype of the mice. Knock-out studies have not been used in chickens so far, but there is some promising development in the area with the CRISPR/Cas9 system (Wang et al. 2017).

2.2 Behavioural genetics and QTL studies on behaviour

Variation in social behaviour, such as pair-bonding, is associated with mutations in the promoter region of the arginine vasopressin receptor (AVPR1a) in humans as well as other species (Walum et al. 2008; Donaldson and Young 2008). A QTL region containing the AVPR1a gene, among others, has been found in the chicken (Wirén and Jensen 2011; Wirén, Wright, and Jensen 2013). The region is

associated with social behaviour and is located on chicken chromosome 1. In *Drosophila*, the sitter and rover phenotypes in larvae are determined by the *for* gene (Osborne et al. 1997). These are some examples where top-down analysis has yielded behavioural genes or regions. Usually it is very difficult to get as far as an actual gene that controls a quantitative trait, especially behaviour, since the traits are most often controlled by several genes with minor effects. Adding to the difficulty is the nature of behavioural traits in that they are usually not straightforward to define and measure reliably. According to Crusio (2015), the most urgent issue in behavioural genetics is that behavioural tests used for evaluating certain behavioural constructs are not properly validated.

In rats selected for tameness, two QTL were found to overlap with the trait (Albert et al. 2009). These QTL additionally overlap with two other QTL for anxiety related traits and adrenal gland weight.

3. The chicken

The chicken (*Gallus gallus*) is commonly believed to have been domesticated about 8,000 years ago in south-east Asia (West and Zhou 1988). One study claims that northern China should also be added to a possible site of chicken domestication based on analyses on ancient DNA from supposed chicken bones (Xiang et al. 2014). This idea has been refuted by a morphological re-evaluation of supposed chicken remains from central and northern China, where the majority of bones were not from chickens, indicating that chickens were not widely kept in those regions (Eda et al. 2016). While Eda et al. (2016) agree that the tropical regions of south-east Asia is a probable origin of chicken domestication, they write that candidate chicken bones need to be analysed with ancient DNA and radiocarbon dating to determine if the samples are actually from the chicken. Peters et al. (2016) also agree that further analyses of supposed chicken remains from across China and east Asia will elucidate the disagreements concerning the temporal and spatial origins of chicken domestication. Taken together, both papers report that the evidence thus far indicates that Northern China is not a probable origin of chicken domestication and that further analysis techniques are required for certain determination (Eda et al. 2016; Peters et al. 2016).

There is a wide variety of the different breeds of chickens today which are used for meat production, entertainment and companionship among other things. The natural habitat of the red junglefowl is very different from the rearing conditions in modern day chicken industry. It consists of forests and semi-open habitats in south-east Asia and the Indian subcontinent (Al-Nasser et al. 2007). Red junglefowls usually organise in smaller groups of individuals (Collias and Collias 1996). The groups are made up of one male with several females, smaller groups of males or solitary males. An average stable for laying hens in the Swedish industry houses 23 000 chickens (Svenskaägg.se). Needless to say, the difference between natural setting and industry housing is clear.

The chicken provides a nice opportunity as an animal model for domestication research. Behaviour researchers often struggle with controlling the environment

of their model species. Chickens offer an opportunity to environmental control already before they are hatched. Eggs can be incubated straight from laying and as chickens are precocial, there is no need for a mother hen. As has already been discussed, minimising the environmental variation is useful when we want to study genes that affect behaviour.

When it comes to domestication genes in chickens, some advancements have been made. The yellow skin gene *BCDO2* (beta-carotene dioxygenase 2) was identified by Eriksson et al. (2008) and it reveals that the domesticated chicken may have a hybrid origin with some inclusion of the grey junglefowl as well as the red junglefowl. A regulatory mutation in *BCDO2* inhibits the expression of the enzyme in only the skin. One study in chickens found a few selective sweeps with possible candidate genes for domestication and *BCDO2* was used as a reference as it was already a known selective sweep in the domesticated birds (Rubin et al. 2010). Selective sweeps are regions in the genome with low diversity (i.e. low heterozygosity), indicative of a selection event. Thyroid stimulating hormone receptor (*TSHR*) was one of the most promising candidate genes found in the selective sweep analysis (Rubin et al. 2010). It is involved in reproduction and metabolic regulation. A mutation in the *TSHR* gene in domesticated chickens seems to affect the reproduction pattern in a way which is characteristic for other domesticated animals and may thus have been an important target in chicken domestication (Karlsson et al. 2016). Another gene that was found in the selective sweep analysis was α-adrenergic receptor 2C (*ADRA2C*) that is associated to stress response regulation. However, upon further investigation, the gene was not found to be correlated to domestication related changes in the stress response of chickens (Elfwing et al. 2014).

Another interesting gene is arginine vasopressin receptor 1a (*AVPR1a*), which is associated to social behaviour. A major growth QTL has been found in chickens, which is in close linkage with *AVPR1a*, and the region correlated with changes in social behaviour of chickens (Wiren et al. 2009). The gene remains an interesting candidate for future research due to its association with social behaviour in other animals. Other candidate genes have been identified as well, e.g. *PMEL17* (Kerje et al. 2004) and *MC1R* (Kerje et al. 2003), which are both associated with plumage colouration.

4. Animal welfare aspects

Intensification of selection for production traits has brought about some problems in respect to animal welfare. As has been discussed in this essay, correlated selection responses can sometimes lead to unpredictable results. For example, intense selection on rapid lean muscle growth in fattening pigs lead to an increased frequency of a mutation in the skeletal muscle ryanodine receptor (*ryr1*), which in turn causes malignant hyperthermia in individuals that are homozygous (Fujii et al. 1991). Malignant hyperthermia can be induced by stress in pigs and can lead to sudden death or poor meat quality, both very costly to the industry. Identification of the *ryr1* gene mutation has made it possible to genotype fattening pigs so that the mutated gene can be avoided in breeding and is no longer a major problem (Hocking, D'Eath, and Kjaer 2011). Another gene

that has been linked to animal welfare issues is *PMEL17* in chickens (Keeling et al. 2004). Individuals with a wild recessive allele in the gene, which controls plumage melanisation (Kerje et al. 2004), are more likely to be victims of intense feather pecking.

Animal welfare is a concept that did not originally arise from science, although it is a scientific concept today (Duncan and Fraser 1997). The origin of animal welfare comes from society as a means to deal with the ethical concerns of how humans treat animals. This means that animal welfare is largely based on ethical values and to properly understand it one must delve into the many ethical views available for explaining what is "right and wrong" when it comes to our treatment of animals. To be able to measure animal welfare, we need a proper definition so that it is clearly stated what it is we are measuring. From a scientific point of view, Broom (2008) writes that "The welfare of an individual is its state as regards its attempts to cope with its environment". This definition states animal welfare in the scientific view as a characteristic of an individual whereas popularly it may be thought of something that is given an individual. In the *ryr1* example, animals with the *ryr1* mutation are clearly less capable of coping with their environment and we can conclude that those animals have a poor welfare.

A popular view of animal husbandry among the public is that animals that have been kept in captivity for a long time have lost either the ability or need to display natural behaviours. Although we can select animals based on traits that will help them cope with the captive environment, care should be taken not to assume that all behaviours can be modified. Behavioural restriction is when animals are not able to perform a natural behaviour, be it one that is usually performed regularly or one for which the motivation may be temporary. Mason and Burn (2011) compare behavioural restriction in animals to that of humans who are placed in e.g. solitary confinement as a punishment. Behavioural problems such as stereotypies often emerge in environments where animals are not able to perform natural behaviours.

5. Summary

Much is yet to be known about the mechanisms behind domestication. Through the use of genetic tools, we are able to identify differences in the genome between for example wild and domesticated species. This information helps us determine the mechanisms underlying domestication. Differentiating between linkage and pleiotropy is an important step in completely understanding the correlated selection effects in domestication. The chicken is an excellent model for domestication research as the wild ancestor is readily available in its natural habitat as well as in captivity. This allows for comparative as well as selection experiments where the domestication process can be replicated. Determining the genetic mechanisms behind animal domestication will not only shed light on this evolutionary process but can also be used to improve animal welfare in a time where increased production rate is highly valued.

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