The Genetic Architecture of Domestication in Animals

Dominic Wright

IFM Biology, AVIAN Behavioural Genomics and Physiology Group, Linköping University, Linköping, Sweden.

Supplementary Issue: Current Developments in Domestic Animal Bioinformatics

ABSTRACT: Domestication has been essential to the progress of human civilization, and the process itself has fascinated biologists for hundreds of years. Domestication has led to a series of remarkable changes in a variety of plants and animals, in what is termed the "domestication phenotype." In domesticated animals, this general phenotype typically consists of similar changes in tameness, behavior, size/morphology, color, brain composition, and adrenal gland size. This domestication phenotype is seen in a range of different animals. However, the genetic basis of these associated changes is still puzzling. The genes for these different traits tend to be grouped together in clusters in the genome, though it is still not clear whether these clusters represent pleiotropic effects, or are in fact linked clusters. This review focuses on what is currently known about the genetic architecture of domesticated animal species, if genes of large effect (often referred to as major genes) are prevalent in driving the domestication phenotype, and whether pleiotropy can explain the loci underpinning these diverse traits being colocated.

KEYWORDS: domestication, genetic architecture, pleiotropy

SUPPLEMENT: Current Developments in Domestic Animal Bioinformatics

CITATION: Wright. The Genetic Architecture of Domestication in Animals. *Bioinformatics and Biology Insights* 2015:9(S4) 11–20 doi: 10.4137/BBI.S28902.

TYPE: Commentary

RECEIVED: June 08, 2015. **RESUBMITTED:** August 24, 2015. **ACCEPTED FOR PUBLICATION:** August 26, 2015.

ACADEMIC EDITOR: J. T. Efird, Associate Editor

PEER REVIEW: Seven peer reviewers contributed to the peer review report. Reviewers' reports totaled 2,129 words, excluding any confidential comments to the academic editor.

FUNDING: DW is supported by grants from the Swedish Research Council (VR) and the Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning (FORMAS), as well as the LiU-Neuro network. The author confirms that the funder had no influence over the study design, content of the article, or selection of this journal.

COMPETING INTERESTS: Author discloses no potential conflicts of interest.

CORRESPONDENCE: domwr@ifm.liu.se

Domestication as a process has been an integral part of human civilization and instrumental in allowing the rapid spread of the human race throughout the globe. Domestication itself is used for a wide variety of analyses and theories, with Darwin himself using it as a model for evolution.[1] More recently, it has helped recreate human migration patterns,[2,3] and the huge phenotypic variation generated in domesticated species have been used to map causal genes and the mutations underlying a variety of trait types.[4] In this way, domestication can aid in completing the genotype–phenotype map in a variety of plants and animals and increase our understanding of how changes in the genome can bring about alterations in both quantitative and discrete traits.

One of the greatest conundrums concerning domestication itself is related to the wide variety of traits that are modified by this selective process. These traits show similar alterations in a wide variety of different domestic species and often the traits themselves seem coincidental or nonbeneficial to the main focus of domestication.[5] This combined domesticated phenotype, as it has been termed,[6] represents a complex of convergent traits. Domestic animals tend to be smaller than their wild counterparts and have reduced or altered pigmentation. Particular pigmental patterns, ranging from albinism, piebaldness, and the like, have all been selected for in a variety of animals.[7,8] More strictly, size has also been selected to be both larger as well as smaller in certain domestic animals, most notably in dogs.[7] Furthermore, different morphological proportions (for example, skull size, shape, and leg length in dogs[7]) have also been selected for. Brain size and composition has also been altered in domestic animals, with an enlarged telencephalon often occurring, and a reduced relative brain size.[9] Behavioral and physiological traits are also often modified. In particular, tameness, also referred to as a reduced fear of human beings in the literature, is increased,[6,10] aggression is decreased, and activity level and explorative tendencies are altered.[11] An earlier onset of sexual maturity,[12–15] increased reproduction (number of estruses, egg production, and the like) and altered adrenal development are all also observed. In animals, it has been posited that selection for tameness was the initial primary focus of domestication. However, it remains to be seen whether there was active selection for all the remaining traits, or whether pleiotropy, drift, relaxed selection, or other forces led to some of them being fixed as well.

Given these markedly different traits that have all been selected for during domestication, a major question is how all these are controlled at the genetic level. Given that selection acting upon such a variety of domestic animals can produce such similar phenotypes, this raises the question of whether this is indicative of how selection acts in all such cases? Are there unique genomic properties of domesticated animals that

allows for such development, or is this solely the product of strong artificial selection? Do domesticated species represent multiple independent case studies of how such selection can progress? To be able to answer these questions, it is necessary to identify the genes behind these different traits (termed the genetic architecture), and how they interact to give rise to the domestic phenotype. First, do genes of large effect give rise to the observed changes, or are they governed by numerous small-effect loci that are additive in nature (as predicted by Fisher). The next question is to what extent is pleiotropy a factor in causing these traits, ie, does one mutation lead to numerous different phenotypic alterations that could help explain the diverse set of changes in the domesticated phenotype? These two questions are examined below.

Major Genes for Domestication

The first stage to the elucidation of the genetic architecture of a trait is generally to identify genes or regions of large effect – often termed major genes. The genetic architecture in this case refers to the number of genes, their effect size, and their location in the genome that govern the variation present in or between any given population. In this context, major genes account for a large percentage of the variation in a given trait. Although appealing because of their relative ease in identification (in comparison to small-effect loci), relatively few examples of major genes for quantitative traits in outbred populations exist.[16] Major genes have been identified in a variety of domestic animals; however, care must be taken in their definition. Many are virtually monogenic in effect, meaning that the trait in question is almost entirely governed by the single gene/mutation in question. For true quantitative traits, the number of major genes identified is far lower, though examples are apparent. The most common example of major genes is for coat color, with the same genes implicated in the regulation of coat color across a variety of different species (including numerous domesticated ones). For example, the genes that have been identified as affecting different coat traits in dogs (most notably *MC1R, ASIP, TYRP1, CBD103*, and *SILV/PMEL17* – see review in Ref. 17) are also found affecting color in a multitude of other species.[18,19] Similarly, the *KIT* gene is associated with white spotting pattern among a variety of color phenotypes in horses,[20] dominant white color in pigs,[21] and proportion of black color in cattle.[22] Such large effects that are exhibited in a cross-species manner is representative of many of these genes for color.[17,23] Coat color is a truly quantitative trait, and while major genes account for a large percentage of the genetic variation of the trait, numerous other genes of much smaller effect are also involved. For example, in the case of the proportion of black coloration in cattle described earlier, although the genes *KIT* and *MITF* and one other locus explained 24% of the variation present, a large number of other loci were required to explain the remaining variation using a genomic prediction model.[22] Therefore, a pertinent question is how many of the major genes identified are really monogenic characteristics, with the gene in question explaining all of the variations in the trait, and how many are part of a wider genetic architecture governing a particular trait. Similarly, the above coat color mutations also highlight how the same gene may be subject to multiple different causal mutations. In the example given earlier, a number of different mutations have affected the same gene in multiple different species (eg, *KIT* and *MC1R*). However, multiple domestication events can potentially lead to different mutations in the same gene in the same species. For example, the *Wx* gene in rice contains multiple mutations affecting the same trait.[24] A breakdown of major genes present in domestic animals is presented below and in Table 1.

Chickens. The comb of the chicken has been a source of interest since the early days of genetics, when Bateson and Punnett used the pea comb, rose comb, and walnut comb mutations to illustrate the first example of Mendelian inheritance and epistasis in animals.[25] These comb mutations were all identified in domesticated chickens and have subsequently been identified at the genomic level.[26,27] Given that these were used as a model of Mendelian inheritance, it is hardly surprising that they are monogenic in effect (although the rose comb and pea comb mutations do interact epistatically to reveal a further comb phenotype – the walnut comb). Other monogenic domestication traits have also been identified in the chicken – principally yellow skin color (controlled by the *BCDO2* gene),[28] duplex comb,[29] and barred coat color genes.[30]

Dogs. In dogs, strong breed differences and extreme inbreeding have aided in the identification of numerous monogenic genes affecting the domesticated phenotype. Genes for wrinkled skin,[31] leg length,[32] and body size[33] have all been discovered. In the case of the last two genes, these traits are also quantitative, though the genes identified explain virtually all the variations between long- and short-legged breeds of dogs, and large and small breeds. Almost all fur growth type and texture phenotypes have also been shown to be explained by only three genes (*FGF5, KRT71*, and *RSPO2*).[34]

Cattle, sheep, and horses. In cattle, a deletion mutation has been identified in the *MSTN* gene that leads to extreme muscular development (an increase in muscle mass of 20%),[35] with the same gene that causes this increased musculature also exhibiting similar effects in sheep.[36] Regarding production traits in cattle, a nonsense mutation in the gene *FMO3* has been identified as causing a characteristic fish-odor in milk from cattle.[37] Also relating to milk production, the *DGAT1* gene accounts for 30% of the variation in fat percentage in milk,[38] while the *ABCG2* gene affects milk composition.[39] Other domestication-related genes have also been identified in the sheep. The gene *RXFP2* has been linked with horn type,[40] though in this case no functional data or mutation identification is currently available to confirm this effect. Also in sheep, an X-linked mutation in a specific breed causes increased ovulation rate and twin births,[41] while an autosomal mutation in *BMPR1B* causes the Booroola phenotype

Table 1. Major genes detected in domestic animals.

ANIMAL	TRAIT	GENE	REFERENCE
Chicken	Pea comb	*SOX5*	26
	Rose comb	*MNR2*	25
	Duplex comb	*EOMES*	28
	Comb size	*HAO1/BMP2*	49
	Yellow skin	*BCDO2*	27
	Barred coat color	*CDKN1A/B*	29
Dog	Wrinkled skin	*HAS2*	30
	Leg length	*FGF4*	31
	Body size	*IGF1*	32
	Fur growth and texture	*FGF5, KRT71, RSPO2*	33
Cattle	Muscle growth	*MSTN*	34
	Milk odor	*FMO3*	36
	Milk production	*DGAT1*	37
	Milk composition	*ABCG1*	38
Sheep	Honr type	*RXFP2*	39
	Increased ovulation rate and twinning	*BMP15*	40
	Booroola and ovulation	*BMPR1B*	41
Horse	Gait type	*DMRT3*	42
Pig	Malignant hyperthermia	*RYR1*	43
	Glycogen content in muscles	*PRKAG3*	44
	Ear size	*PPARD*	46
	Muscularity and backfat	*IGF2*	45
	Meat tenderness	*CAST*	47

that also affects ovulation.[42] In horses, the gene *DMRT3* has recently been shown to be required for the unique gait types present in Icelandic horses.[43] In the case of the *DMRT3* locus, this is particularly intriguing as it is probably the only major gene identified in domestic animals that can be thought of as modifying behavior.

Pigs. In pigs, a major gene for malignant hyperthermia has been associated with the *ryr1* gene[44] that also controls meat quality traits, while a nonconservative mutation in the gene *PRKAG3* leads to high glycogen content in muscles.[45] A gene affecting muscularity has also been identified in pigs (*IGF2*), which also affects back fat and heart size,[46] while the gene *PPARD* has been identified as affecting ear size.[47] In both the latter cases, the traits are fully quantitative, yet the identified genes account for a large percentage of the trait variation – 40% in the case of *PPARD* and 15%–30% in the case of *IGF2*. Polymorphisms in the *CAST* gene have also been associated with meat tenderness in pigs, though more in-depth functional assays have yet to be made beyond this association.[48]

Quantitative trait loci studies. In the examples shown earlier, the bulk of major genes identified act in a monogenic fashion, in that they explain almost all the variation of the traits they regulate. A few of the genes in question are part of the architecture of a standard quantitative trait, though certainly examples are present (as discussed earlier). In terms of analyzing whether major genes are more prevalent in domesticated species, it is important to bear in mind that the identification of the actual causal genes or mutation is extremely rare. In contrast, more standard Quantitative Trait Loci (QTL) mapping studies can be used to identify the overall genetic architecture of a trait in terms of estimating the number of loci involved and their relative strength of effect.[49] Such studies are far more abundant and still give an idea of the underlying architecture. There are, of course, problems with this approach. The use of an F_2 or similar type of second-generation intercross population means that the resolution in terms of the size of the QTL regions identified is far too low for candidate gene identification. Each QTL typically covers a span of ~20–30 cM, depending on the size of the cross, which can equate to hundreds or thousands of genes, depending on the genome size and recombination rate of the species used. This low resolution, caused by the limited number of recombinations that have accrued in these intercross populations, can also lead to a misleadingly simplified genetic architecture. This potential problem occurs when a QTL is in fact made up of multiple smaller loci; however because of the low number of recombinations present in the population and hence the

poor resolution, these manifest as a larger effect and would be falsely described as a major gene/QTL effect. Similarly, if the loci are antagonistic (ie, have the opposite direction of effect in terms of the additive effect of each sublocus), a QTL may be missed. Nevertheless, the relative ease of performing a QTL analysis means the number of identified loci and the number of successful studies are very high, allowing a more holistic examination of the prevalence of major genes (or rather major-effect QTL). Table 2 lists the current genome build and online QTL resources for the domestic animals listed below.

In the chicken, major-effect loci have been identified for comb mass,[50] growth,[13,51] and susceptibility to feather pecking.[52] In contrast, most other traits measured in domestic chickens compared to their wild counterparts show more standard effect sizes (mean ~5%)[49,53] and no large-effect genes have been found in traits ranging from bone allocation,[54,55] fear-avoidance behavior,[12,56] onset of sexual maturity,[15] number of eggs produced,[57] and production characteristics (muscle pH, color, and egg taste).[58]

In pigs, QTL for a wide variety of production-related traits have been identified, including teat number,[59] porcine leukocyte count,[60] carcass quality and growth traits,[61–63] meat quality[64] and pH,[64] litter size/fecundity,[65] and disease resistance.[66] There are well over 100 QTL studies involving the pig, with the results summarized in several reviews[65–67] and a pig QTL database.[68] Some large-effect QTL have been observed, including loci for shoulder weight, loin weight and ham weight,[63] and pH,[64] with the rest being standard effect sizes.

A multitude of QTL studies in cattle have looked at characteristics such as growth, meat quality, milk composition, behaviour, fecundity and reproduction, mastitis and pigmentation. For a full summary, the bovine QTL website (http://bovinegenome.org/bovineqtl_v2/login.jsp) gives a full list of location, effect, and breed, among other information. Of the QTL, once again the majority are of standard (ie, relatively modest) effect sizes, though milk composition and pigmentation traits contained major loci (with the genes identified, as discussed earlier).

Summary of major genes in domestication. A common pattern occurs in almost all the domestic species – although some major genes are present, this does not appear to be the norm for the bulk of the loci that affect these domestication characters. The fact that such loci are present at all is most likely because of the strong directional selection brought about by domestication, as it would be relatively easy to identify and fix such polymorphisms/mutations as they are phenotypically identified. Further evidence for this directional selection favoring some major gene effects is also provided by the genetic architecture of morphology in the dog. The dog has undergone some of the most extreme directional selection among domesticated animals, leading to the most phenotypically diverse mammalian species on the planet.[69] This selection, in combination with the extreme inbreeding within breeds, appears to have led to a remarkably simple genetic architecture, especially for morphological traits. Numerous monogenic mutations have therefore arisen in the dog and aided gene identification, while even more standard morphological studies tend to have >70% of the variation explained by two to six QTL.[70] Reasons posited for this simplistic architecture have been based on the fact that many modern breeds were created during the Victorian era, when breeders focused heavily on novelty and the preservation of discrete mutations.[70] Such discrete mutations would then be easy to breed into a variety of different genetic backgrounds, which then expanded the breed diversity. This is potentially at odds with the selection occurring in other domesticated breeds, where selection instead is being directed on economically important traits by using the standing genetic variation already present within a wild population, rather than large-effect discrete

Table 2. Genome build and QTL resources for domestic animals.

ANIMAL	GENOME BUILD	QTL RESOURCES	WEBSITE/REFERENCE
Chicken	galGal4 (2011)	ArkDB	www.thearkdb.org[122]
		Chich_VD_seq	http://chicken.genomics.org.cn[123]
		QTLdb	http://www.animalgenome.org/cgi-bin/QTLdb/index[124]
Pig	susScr3 (2011)	PigQTLDB	[68]
		Pig Genome Database (PiGenome)	http://pigenome.nabc.go.kr/[125]
		ArkDB	www.thearkdb.org[122]
		QTLdb	http://www.animalgenome.org/cgi-bin/QTLdb/index[124]
Cattle	bosTau8 (2014)	Bovine QTL viewer	http://bovinegenome.org/bovineqtl_v2/login.jsp[126]
		Cattle QTL Database	http://www.bfro.uni-lj.si/Kat_genet/genetika/mammary_gland.xls[127]
		ArkDB	www.thearkdb.org[122]
		QTLdb	http://www.animalgenome.org/cgi-bin/QTLdb/index[124]
Sheep	oviAri3 (2012)	QTLdb	http://www.animalgenome.org/cgi-bin/QTLdb/index[124]
Dog	canFam3 (2011)	NA	NA

mutations. This would then imply that the large-effect genes that have been identified across domesticated species are more recent mutations that were far easier to select on, whereas the bulk of the variation present in a domestic species came from the standing variation present in the wild progenitors.

Pleiotropy of Domestication Effects

One of the most enduring questions regarding the domestication process has been the recurrent evolution of a discrete set of traits that make up the domestication phenotype. Darwin himself first noted this when examining domestic mammals in relation to their wild counterparts[1] and was drawn on whether this was because of something in the domestication process per se. In this role, domestication could serve as a general model for convergent evolution when species undergo strong directional selection.[71] As stated earlier, the domestication syndrome itself tends to comprise changes in tameness, coat color/pigmentation, skull morphology, reproductive alterations, hormone and neurotransmitter concentrations, and brain composition. Given these changes, it is therefore possible that the common domestic environment induces this suite of alterations or that the genes under selection have pleiotropic effects on multiple traits. Most pertinently, domestication has been posited to initially be driven by selection for tameness.[10,72] One early potential theory for these domestication phenotypes are through common environmental effects, what Darwin referred to as gentler conditions of living in the domestics causing these changes.[1,73] However, the evidence for such environmental effects is very sparse. Heritability estimates of different domestication traits reveal a strongly heritable component on the behavior and morphology traits associated with domestication,[74,75] which would not occur if these were environmentally driven. Further, feral populations of wild-living domesticates do not show the complete loss of the phenotypes fixed during domestication, though this is complicated by hybridization with wild species.[76] For example, feral chickens that live in Hawaii have been shown to maintain signatures of both color and vocalization in their current state, despite having hybridized with the progenitor Red Junglefowl on the island.[77] In relation to pleiotropy, further hypotheses have also been posited. Most recently, a role has been proposed for neural crest cells (NCCs) driving the changes, with this based on the reduced size and function of the adrenal glands.[78] A further theory, also based on this alteration in adrenal size, hypothesizes that the domestication phenotype is because of a single genetic regulatory network, with the main genetic changes occurring in upstream regulators, and thereby affecting a large number of diverse downstream systems.[79] The common denominator for both these hypotheses is obviously that the changes induced are actually pleiotropic and affect many different traits.

Evidence for pleiotropy in domestication. Perhaps the best evidence for pleiotropy is the correlations that exist between separate components of the domestication syndrome when domestication is recreated through selection lines. The most well known of these selection lines was based on the silver fox and consisted of directional selection solely based on tameness and aggression.[72,80] It was found that after only 8–10 generations, color changes appeared (yellowing and piebaldness), adults maintained the juvenile floppy ears, skull changes occurred (leading to short and wide faces), as did curly tails.[79,81] These results suggest that selection on a single behavioral trait can lead to a range of morphological changes. In a similar experiment, rats also divergently selected for tameness/aggression exhibited changes in neurotransmitters, hormone levels, and morphology.[82,83] These studies imply that the loci for tameness show pleiotropic effects on multiple different domestication syndrome traits, though in these instances close linkage between different genes affecting each trait could also be a potentially plausible explanation.

If pleiotropy is occurring, QTL studies between wild and domestic animals should show an overlap between the multiple different domestication traits. Plant and animal studies using this mapping approach show a marked similarity in their findings. Multiple domestication traits are found clustered fairly closely together throughout the genome. These clusters are fairly loose, typically ≥20–30 cM (1 cM roughly equates to a 1% recombination rate, with the physical distance varying depending on the species in question – in human beings and mice, in a standard design, 1 cM is ~1 Mb; in chickens, 1 cM is ~350 kb). In plants, these clusters have been found in beans,[84,85] maize,[86,87] sunflowers,[88] rice,[89] and pearl millet.[90] Initial work using the aforementioned rat selection lines found that when divergent lines were crossed together to map the underlying genes, clusters of QTL were also once again revealed. In the case of the rat, these were in two clusters spanning 41 and 29 cM, respectively.[82] Using an intercross between wild and domestic chickens, QTL clusters were found that indicated multiple different trait types were overlapping,[13] with loci for comb size (a sexually selected ornament in the chicken) overlapping with onset of sexual maturity loci,[15] as well as with bone density and egg production traits.[57] In the silver foxes differentially selected for behavior (also mentioned previously), a QTL analysis for behavior indicated an overlap between different behavioral QTL, though this study was restricted to behavioral traits, so other characteristics were not mapped simultaneously.[91]

The problem with these examples is related to the mechanics of QTL analysis as it is generally performed. All these studies use variations on an F_2 intercross, meaning that the resolution of such studies tends to be rather low, with the confidence intervals (~30 cM or more) equating to at least this number of megabases in almost all the species examined. Loci can be overlapping but this may be because of linkage (ie, close physical proximity between loci) rather than direct pleiotropy from a single causal loci. For example, in the case of the wild x domestic chicken study, statistical analysis aimed at separating these two states found that most clusters in the

F_2 population appeared to be due to linkage, with only the central core of QTL in each cluster unable to be distinguished as either closely linked or pleiotropic.[13] To ascertain if true pleiotropy is occurring in such clusters, there are a number of techniques that can be used. First, you can attempt to increase the number of recombinations to expand the genetic map, by intercrossing for further generations (thereby increasing the resolution of the detected QTL).[92] If these loci are pleiotropic, then the clusters should remain the same size, rather than expanding along with the map. In the case of the chicken intercross, this was expanded to eight generations of intercrossing, with the result being far narrower intervals generated. One such locus affecting comb size was reduced to 600 kb, with only two genes in the interval, and with expression analyses indicating greater effects from one gene, *HAO1*.[50] This gene was also found to show pleiotropic effects on bone and egg production characteristics, once again using a combination of QTL analysis and gene expression correlations between the traits and genes involved. When a more global expression QTL (eQTL) analysis of both comb and bone samples was performed (enabling multiple genes to be tested for effects on expression in both comb and bone tissue), results suggested that both pleiotropy and linkage were present.[93]

To truly define pleiotropy, however, the actual causal mutation/polymorphism must be identified. In this instance, it is possible to identify genuine pleiotropic effects. Unfortunately, as shown earlier, the identification of such loci is extremely rare. More plant-based examples exist than their animal counterparts, and even here, the polymorphisms that are more readily identified are most commonly of very large effect. This makes them almost functionally identical to major genes rather than the small-effect loci more commonly associated with quantitative traits. Although this review focuses on animal domestication, plant genetics has some surprising and relevant results to elucidate the mechanisms at work. Where polymorphisms have been identified, there appears to be pleiotropy. The Q locus in wheat affects a variety of traits, including free-threshing and floral development characteristics,[94,95] and the *tb1* locus in maize affects a variety of domestication characters.[87,96] However, in the case of *tb1*, there are also other mutations in linked loci that affect domestication traits.[86,87] Other examples demonstrate that, in fact, different mutations can be present in close proximity. The shattering mutation in rice is a single recessive mutation that is tightly linked to loci affecting seed dormancy and the pericarp.[97] Animal examples of the identification of the causal mutation for a quantitative trait in a domestic animal includes the *IGF2* mutation in pigs, which also affects muscle mass and fat deposition.[46] Somewhat strikingly, many of the other mutations identified in animals do not exhibit extensive pleiotropy, and certainly none of the extreme pleiotropy that would be required to explain some of the more diverse aspects of the domestication syndrome. Therefore, it seems that if one considers both plant and animals examples, pleiotropy does exist, and also that domestication mutations often exist in linked groups of multiple mutations/genes (certainly in the case of plant domestication genetic architecture).

It is also of interest to compare the extent of pleiotropy as seen in domestication with that observed in quantitative traits in general. One issue here is that there are several different types of quantitative traits (morphological, behavioral, and life history in general) that may be under very different forms of selection. The extent of pleiotropy present in general was thought to be high because of predictions based on extensions of Fisher's geometric model. This led to the universal pleiotropy hypothesis that states that pleiotropy arises so frequently as to almost be considered universal.[98] Pleiotropy is also the foundation of the cost of complexity hypothesis, which posits that complex organisms are less adaptable or responsive to evolution because of the increased degree of pleiotropy that is present.[99,100] However, despite these hypotheses,[98] QTL studies in general have found there to be less pleiotropy than expected (see pleiotropic scans in mice[101] and stickleback[102]). Similarly, empirical data from gene knockout and knockdown experiments in a variety of taxa ranging from yeast to mice also indicates that pleiotropy is generally fairly low (see the review by Wagner and Zhang[103]). It therefore appears that domestication traits do not appear to exhibit more pleiotropy than quantitative traits in general, though with the caveat that additional mutation identification is most likely required to verify this statement.

Phenotypic buffering, eQTL, and pleiotropy. Phenotypic buffering was first proposed by Waddington and was initially used to explain how the phenotype of an animal could be resilient to genetic and environmental perturbations.[104] This idea has recently been taken into account for potential pleiotropy in eQTL analyses – if buffering is correct, then when certain key loci are perturbed, this will lead to a raft of other changes being revealed. The underlying mutations would no longer be buffered, hence their effects would then be revealed by the single buffering locus alteration. eQTL analysis itself consists of standard QTL mapping, though in this instance uses global gene expression from a particular tissue as the source of the phenotypes. By combining these with the genotypic information of each individual, it is possible to map genes that vary according to their underlying genotype. This should then be observed by hotspots in the eQTL with multiple trans effects, showing genes from dispersed areas of the genome are all controlled by a single genetic locus.[105,106] Although the resolution issues of QTL analysis can once again be an issue here, the phenotype (gene expression) tends to be less noisy than conventional analysis. Where such analysis has been performed, pleiotropic hotspots appear to be rather limited, even when they are found. For example, in the study by Fu et al,[106] several phenotypic hotspots were found, as were hotspots for metabolite abundance; yet, these were only reflected in a single eQTL hotspot. Chesler et al found a relatively small number of QTL correlated with large gene expression modules situated

in the genome, hypothesizing that this indicated pleiotropy.[107] If multitrait pleiotropy for the domestication syndrome does exist, then obviously such eQTL hotspots should also be observed in wild × domestic intercross eQTL analyses. In the case of the rat lines divergently selected for tameness, an eQTL analysis was performed on 150 individuals and only identified one locus that contained more trans eQTL than was expected by chance, with this being only just significant (seven in the region and six expected by chance),[108] with this hotspot not overlapping any of the tameness QTL. In the case of the chicken, multiple tissues have been used for this type of eQTL analysis. In bone samples, some trans hotspots occurred, though most did not overlap any of the bone QTL observed.[55] Therefore, a similar pattern is once again seen as with major gene pleiotropy.

Domestication by Modules

Given that although pleiotropy does occur, its effects seem somewhat limited and cannot alone explain the large clusters of multiple different trait QTL all grouping in loose clusters throughout the genome. The most parsimonious explanation is therefore that linked genes surround a pleiotropic core in each of these clusters or modules. The population geneticist Grant noticed how in plants even a strong domestication phenotype could be rapidly broken down during reverse selection or through cross-breeding.[109] This is similar to what has been shown in animal examples.[13,108,110] This system would allow the rapid introgression of desirable traits into a domesticated species, with the remainder of the domesticated phenotype easily recapitulated in this new hybrid. It still remains to be ascertained whether such a system of linkages is specific to domesticated species (and therefore has the potential to help explain why so relatively few species have been domesticated, despite multiple opportunities existing for additional species) or is in fact a more general effect brought about by directional selection.

Modularity is found not only with loci affecting different aspects of the domestic phenotype but can also be seen with gene expression in general and how the genome is organized. For example, although it appears that hundreds or even thousands of genes govern the differences between wild and domestic populations, judging by the gene expression changes seen in microarrays,[111–113] these genes tend to be located in discrete clusters or modules. Therefore, genes with similar expression patterns are located in close proximity. A particularly interesting study by Litvin and colleagues[114] combined both eQTL analysis and clustering analysis. By first identifying where genes were clustered together in the genome, in terms of sharing similar expression patterns, they then went on to use this to identify genes that were controlled by multiple different loci. In this case, 44 different modules were detected throughout the genome (with each module linking five or more genes), so a relatively small number of modules tie in the majority of gene expression differences between wild and domestic yeast. It also showed that multiple interacting loci influence the expression of these modules as opposed to one single pleiotropic locus for each cluster. A similar pattern has been observed using wild inbred lines of *Drosophila*,[115] with differentially expressed genes grouped together in clusters in the genome.

It is possible to model how linkage blocks may evolve. Using a model of allogamous and autogamous species, D'Ennequin demonstrated that by starting with loci distributed evenly throughout the genome for a variety of traits, continuous selection can lead to clusters of QTL forming in the genome, with between two and four loci linked together in each cluster in their model.[116] This mimicked the observed effects seen in a variety of domestic plants and animals. The authors of that study draw parallels between gene clusters for domestication and those for Batesian mimicry in butterflies. In the case of Batesian mimcry, genes affecting various aspects of mimicry phenotypes are all grouped together in supergenes.[117] Any recombinants are therefore strongly selected against, as they will be poorer mimics. A mechanism that has been proposed to explain this development is the sieve hypothesis,[118] and there is, therefore, a great deal of support for such clustering, both empirically (from assorted QTL studies) and theoretically.

Concluding Remarks

The huge changes brought about by domestication selection provide us with a puzzle as to how the domestication phenotype appears to have been replicated in so many distinctly different species. Questions as to how these changes are brought about at the genetic level and whether they are typical of directional selection in general, or rather represent a specific case, have yet to be fully addressed. Perhaps most intriguing is the thought that certain species may contain the right genomic makeup, allowing them to be more easily domesticated, whereas others will be almost impossible to domestic for the same reason.

Several different theories have been raised to potentially explain how the domesticated phenotype develops genetically, and how multiple diverse characteristics are selected and fixed in the genome. These theories can be broadly divided into the 'neural crest hypothesis'[76], the 'single genetic network' hypothesis[77] and what I have termed the 'clustered linkage' hypothesis (after a theory first posited by Grant[109]). The neural crest hypothesis posits that mild neural crest deficits during embryonic development can drive the diverse range of phenotypes affected by the domestication syndrome. NCCs are precursor cells for a wide variety of tissue types,[119,120] so domestication selection for behavior could be targeting genetic variants that modify NCC numbers or migration, which in turn leads to a variety of pleiotropic effects. The single genetic network hypothesis is built on a theory developed by Belyaev,[72] whereby reduced stress levels in the domestic environment leads to hormonal responses that reset

gene expression patterns. This theory has then been expanded to a single genetic regulatory network underlying the domesticated phenotype. Mutations or polymorphisms are then selected for upstream regulators of the network, resulting in numerous downstream changes.[79] These upstream mutations can be genetic or epigenetic in nature. Finally, the clustered linkage hypothesis has been outlined in detail earlier. Of the three, the first two predict strong and diverse (in terms of the traits affected) pleiotropy, while the third suggests that linkage is the most dominant factor at play. When weighing up the current evidence, it is noteworthy that, although present, pleiotropy does not appear to be so widespread in domesticated species as is predicted by the first two hypotheses. When pleiotropy is found, the traits affected tend to be those that are related functionally, for example, different aspects of bone physiology, etc. They do not appear to explain the more diverse aspects of domestication (eg, behavior and morphology), when either the causal gene is known or fine-scale QTL analysis is used. In contrast, clusters of QTL have been identified in the genomes of multiple different domesticated plant and animal species. Similarly, eQTL analysis also finds multiple modules/clusters but less pleiotropy. Therefore, the current evidence appears to be against the neural crest and genetic network hypotheses and in favor of the linkage clusters. As a slight modification to the latter theory, I would suggest that a pleiotropic core surrounded by more loosely linked loci would best explain the observed data and is the most parsimonious explanation. However, until the actual mutations underlying the diverse traits that make up the domestication phenotype are revealed, it will be impossible to verify this extension.

The advances in genomic resources can only aid the field of domestication genetics and the identification of the genetic architecture that underlies it. High-density SNP chips allow Genome Wide Association Studies to be more easily performed on pedigree populations, removing the need for tailored intercrosses. This is especially useful for large animals with longer generation times. Genetic sequencing has reduced greatly in price and a variety of domestication 1000 genomes projects have started with a view to mapping variants within species.[121] Similarly, transcriptomic, methylomic, and other forms of sequence mapping (CHIP-seq, siRNA-seq, and the like) raise the possibility to gain a holistic view of the raft of potential changes underpinning domestication.

Acknowledgments

The author would like to thank Dr. R. Henriksen for valuable comments on the manuscript.

Author Contributions

Wrote the first draft of the manuscript: DW. Developed the structure and arguments for the paper: DW. Made critical revisions: DW. The author reviewed and approved of the final manuscript.

REFERENCES

1. Darwin C. The Variation of Animals and Plants under Domestication. London: John Murray; 1868.
2. Gerbault P, Allaby RG, Boivin N, et al. Storytelling and story testing in domestication. *Proc Natl Acad Sci U S A*. 2014;111(17):6159–64.
3. Evin A, Flink LG, Bălăşescu A, et al. Unravelling the complexity of domestication: a case study using morphometrics and ancient DNA analyses of archaeological pigs from Romania. *Philos Trans R Soc Lond B Biol Sci*. 2015;370(1660):20130616.
4. Andersson L, Georges M. Domestic animal genomics: deciphering the genetics of complex traits. *Nat Rev Genet*. 2004;5:202–12.
5. Brown TA, Jones MK, Powell W, Allaby RG. The complex origins of domesticated crops in the fertile crescent. *Trends Ecol Evol*. 2009;24(2):103–9.
6. Price EO. *Animal Domestication and Behaviour*. Wallingford, CT: CABI Publishing; 2002.
7. Clutton-Brock J. *A Natural History of Domesticated Mammals*. Cambridge University Pressm, Cambridge; 1999.
8. Mosher DS, Quignon P, Bustamante CD, et al. A mutation in the myostatin gene increases muscle mass and enhances racing performance in heterozygote dogs. *PLoS Genet*. 2007;3(5):e79.
9. Kruska D. The effect of domestication on brain size and composition in the mink (Mustela vison). *J Zool*. 1996;239(4):645–61.
10. Jensen P, Wright D. Behavioral genetics and animal domestication. In: Grandin T, Deesing MJ, eds. *Genetics and Behavior of Domestic Animals*. London: Academic Press; 2014:41–80.
11. Schutz KE, Jensen P. Effects of resource allocation on behavioural strategies: a comparison of red junglefowl (*Gallus gallus*) and two domesticated breeds of poultry. *Ethology*. 2001;107(8):753–65.
12. Schutz K, Kerje S, Carlborg O, Jacobsson L, Andersson L, Jensen P. QTL analysis of a red junglefowl x white Leghorn intercross reveals trade-off in resource allocation between behavior and production traits. *Behav Genet*. 2002;32(6):423–33.
13. Wright D, Rubin CJ, Martinez Barrio A, et al. The genetic architecture of domestication in the chicken: effects of pleiotropy and linkage. *Mol Ecol*. 2010;19(23):5140–56.
14. Boitani L, Ciucci P. Comparative social ecology of feral dogs and wolves. *Ethol Ecol Evol*. 1995;7(1):49–72.
15. Wright D, Rubin C, Schutz K, et al. Onset of sexual maturity in female chickens is genetically linked to loci associated with fecundity and a sexual ornament. *Reprod Domest Anim*. 2012;47:31–6.
16. Glazier AM, Nadeau JH, Aitman TJ. Finding genes that underlie complex traits. *Science*. 2002;298(5602):2345–9.
17. Schmutz S, Berryere T. Genes affecting coat colour and pattern in domestic dogs: a review. *Anim Genet*. 2007;38(6):539–49.
18. Kijas J, Wales R, Törnsten A, Chardon P, Moller M, Andersson L. Melanocortin receptor 1 (MC1R) mutations and coat color in pigs. *Genetics*. 1998;150(3):1177–85.
19. Rieder S, Taourit S, Mariat D, Langlois B, Guérin G. Mutations in the agouti (ASIP), the extension (MC1R), and the brown (TYRP1) loci and their association to coat color phenotypes in horses (Equus caballus). *Mamm Genome*. 2001;12(6):450–5.
20. Haase B, Brooks S, Tozaki T, et al. Seven novel KIT mutations in horses with white coat colour phenotypes. *Anim Genet*. 2009;40(5):623–9.
21. Moller MJ, Chaudhary R, Hellmen E, Höyheim B, Chowdhary B, Andersson L. Pigs with the dominant white coat color phenotype carry a duplication of the KIT gene encoding the mast/stem cell growth factor receptor. *Mamm Genome*. 1996;7(11):822–30.
22. Hayes BJ, Pryce J, Chamberlain AJ, Bowman PJ, Goddard ME. Genetic architecture of complex traits and accuracy of genomic prediction: coat colour, milk-fat percentage, and type in Holstein cattle as contrasting model traits. *PLoS Genet*. 2010;6(9):e1001139.
23. Cieslak M, Reissmann M, Hofreiter M, Ludwig A. Colours of domestication. *Biol Rev Camb Philos Soc*. 2011;86(4):885–99.
24. Choudhury BI, Khan ML, Dayanandan S. Patterns of nucleotide diversity and phenotypes of two domestication related genes (OsC1 and Wx) in indigenous rice varieties in Northeast India. *BMC Genet*. 2014;15(1):71.
25. Bateson, W, Punnett RC. (1905). A suggestion as to the nature of the "walnut" comb in fowls. *Proc Camb Phil Soc*. 13, 165–68.
26. Imsland F, Feng C, Boije H, et al. The rose-comb mutation in chickens constitutes a structural rearrangement causing both altered comb morphology and defective sperm motility. *PLoS Genet*. 2012;8(6):e1002775.
27. Wright D, Boije H, Meadows JR, et al. Transient ectopic expression of SOX5 during embryonic development causes the Pea-comb phenotype in chickens. *PLoS Genet*. 2009;5(6):e1000512.
28. Eriksson J, Larson G, Gunnarsson U, et al. Identification of the yellow skin gene reveals a hybrid origin of the domestic chicken. *PLoS Genet*. 2008;4(2):e1000010.
29. Dorshorst B, Harun-Or-Rashid M, Bagherpoor AJ, et al. A genomic duplication is associated with ectopic eomesodermin expression in the embryonic chicken comb and two duplex-comb phenotypes. *PLoS Genet*. 2015;11(1):e1004947.

30. Hellström AR, Sundström E, Gunnarsson U, et al. Sex-linked barring in chickens is controlled by the CDKN2 A/B tumour suppressor locus. *Pigment Cell Melanoma Res*. 2010;23(4):521–30.
31. Olsson M, Meadows JR, Truvé K, et al. A novel unstable duplication upstream of HAS2 predisposes to a breed-defining skin phenotype and a periodic fever syndrome in Chinese Shar-Pei dogs. *PLoS Genet*. 2011;7(3):e1001332.
32. Parker HG, VonHoldt BM, Quignon P, et al. An expressed fgf4 retrogene is associated with breed-defining chondrodysplasia in domestic dogs. *Science*. 2009;325(5943):995–8.
33. Sutter NB, Bustamante CD, Chase K, et al. A single IGF1 allele is a major determinant of small size in dogs. *Science*. 2007;316(5821):112–5.
34. Cadieu E, Neff MW, Quignon P, et al. Coat variation in the domestic dog is governed by variants in three genes. *Science*. 2009;326(5949):150–3.
35. Grobet L, Martin LJ, Poncelet D, et al. A deletion in the bovine myostatin gene causes the double-muscled phenotype in cattle. *Nat Genet*. 1997;17(1):71–4.
36. Clop A, Marcq F, Takeda H, et al. A mutation creating a potential illegitimate microRNA target site in the myostatin gene affects muscularity in sheep. *Nat Genet*. 2006;38(7):813–8.
37. Lundén A, Marklund S, Gustafsson V, Andersson L. A nonsense mutation in the FMO3 gene underlies fishy off-flavor in cow's milk. *Genome Res*. 2002;12(12):1885–8.
38. Grisart B, Coppieters W, Farnir F, et al. Positional candidate cloning of a QTL in dairy cattle: identification of a missense mutation in the bovine DGAT1 gene with major effect on milk yield and composition. *Genome Res*. 2002;12(2):222–31.
39. Cohen-Zinder M, Seroussi E, Larkin DM, et al. Identification of a missense mutation in the bovine ABCG2 gene with a major effect on the QTL on chromosome 6 affecting milk yield and composition in Holstein cattle. *Genome Res*. 2005;15(7):936–44.
40. Johnston SE, McEwan JC, Pickering NK, et al. Genome-wide association mapping identifies the genetic basis of discrete and quantitative variation in sexual weaponry in a wild sheep population. *Mol Ecol*. 2011;20(12):2555–66.
41. Galloway SM, McNatty KP, Cambridge LM, et al. Mutations in an oocyte-derived growth factor gene (BMP15) cause increased ovulation rate and infertility in a dosage-sensitive manner. *Nat Genet*. 2000;25(3):279–83.
42. Souza C, MacDougall C, Campbell B, McNeilly A, Baird D. The Booroola (FecB) phenotype is associated with a mutation in the bone morphogenetic receptor type 1 B (BMPR1B) gene. *J Endocrinol*. 2001;169(2):R1–6.
43. Andersson LS, Larhammar M, Memic F, et al. Mutations in DMRT3 affect locomotion in horses and spinal circuit function in mice. *Nature*. 2012;488(7413):642–6.
44. Fujii J, Otsu K, Zorzato F, et al. Identification of a mutation in porcine ryanodine receptor associated with malignant hyperthermia. *Science*. 1991;253(5018):448–51.
45. Milan D, Jeon JT, Looft C, et al. A mutation in PRKAG3 associated with excess glycogen content in pig skeletal muscle. *Science*. 2000;288(5469):1248–51.
46. Van Laere AS, Nguyen M, Braunschweig M, et al. A regulatory mutation in IGF2 causes a major QTL effect on muscle growth in the pig. *Nature*. 2003;425(6960):832–6.
47. Ren J, Duan Y, Qiao R, et al. A missense mutation in PPARD causes a major QTL effect on ear size in pigs. *PLoS Genet*. 2011;7(5):e1002043.
48. Meyers S, Beever J. Investigating the genetic basis of pork tenderness: genomic analysis of porcine CAST. *Anim Genet*. 2008;39(5):531–43.
49. Falconer, DS, Mackay TFC. Introduction to Quantitative Traits. 4th edn. Harlow, UK. Longman; 1996.
50. Johnsson M, Gustafson I, Rubin CJ, et al. A sexual ornament in chickens is affected by pleiotropic alleles at HAO1 and BMP2, selected during domestication. *PLoS Genet*. 2012;8(8):e1002914.
51. Kerje S, Carlborg O, Jacobsson L, et al. The twofold difference in adult size between the red junglefowl and white Leghorn chickens is largely explained by a limited number of QTLs. *Anim Genet*. 2003;34(4):264–74.
52. Keeling L, Andersson L, Schütz KE, et al. Chicken genomics: feather-pecking and victim pigmentation. *Nature*. 2004;431(7009):645–6.
53. Flint J. Analysis of quantitative trait loci that influence animal behaviour. *J Neurobiol*. 2003;54:46–77.
54. Rubin C-J, Brändström H, Wright D, et al. Quantitative trait loci for BMD and bone strength in an intercross between domestic and wildtype chickens. *J Bone Miner Res*. 2007;22(3):375–84.
55. Johnsson M, Jonsson KB, Andersson L, Jensen P, Wright D. Genetic regulation of bone metabolism in the chicken: similarities and differences to mammalian systems. *PLoS Genet*. 2015;11(5):e1005250.
56. Schütz KE, Kerje S, Jacobsson L, et al. Major growth QTLs in fowl are related to fearful behavior: possible genetic links between fear responses and production traits in a red junglefowl x white Leghorn intercross. *Behav Genet*. 2004;34(1):121–30.
57. Wright D, Kerje S, Brändström H, et al. The genetic architecture of a female sexual ornament. *Evolution*. 2008;62:86–98.
58. Wright D, Kerje S, Lundström K, et al. Quantitative trait loci analysis of egg and meat production traits in a red junglefowl x white Leghorn cross. *Anim Genet*. 2006;37:529–34.
59. Rodríguez C, Tomás A, Alves E, et al. QTL mapping for teat number in an Iberian-by-Meishan pig intercross. *Anim Genet*. 2005;36(6):490–6.
60. Edfors-Lilja I, Wattrang E, Andersson L, Fossum C. Mapping quantitative trait loci for stress induced alterations in porcine leukocyte numbers and functions. *Anim Genet*. 2000;31(3):186–93.
61. Nezer C, Moreau L, Wagenaar D, Georges M. Results of a whole genome scan targeting QTL for growth and carcass traits in a pietrain x large white intercross. *Genet Sel Evol*. 2002;34(3):371–88.
62. Varona L, Ovilo C, Clop A, et al. QTL mapping for growth and carcass traits in an Iberian by Landrace pig intercross: additive, dominant and epistatic effects. *Genet Res*. 2002;80(02):145–54.
63. Milan D, Bidanel JP, Iannuccelli N, et al. Detection of quantitative trait loci for carcass composition traits in pigs. *Genet Sel Evol*. 2002;34(6):705–28.
64. Sanchez MP, Riquet J, Iannuccelli N, et al. Effects of quantitative trait loci on chromosomes 1, 2, 4, and 7 on growth, carcass, and meat quality traits in backcross Meishan × large white pigs. *J Anim Sci*. 2006;84(3):526–37.
65. Buske B, Sternstein I, Brockmann G. QTL and candidate genes for fecundity in sows. *Anim Reprod Sci*. 2006;95(3):167–83.
66. Jørgensen CB, Cirera S, Anderson SI, et al. Linkage and comparative mapping of the locus controlling susceptibility towards *E. coli* F4ab/ac diarrhoea in pigs. *Cytogenet Genome Res*. 2002;102(1–4):157–62.
67. Rothschild MF, Hu ZL, Jiang Z. Advances in QTL mapping in pigs. *Int J Biol Sci*. 2007;3(3):192–7.
68. Hu ZL, Dracheva S, Jang W, et al. A QTL resource and comparison tool for pigs: PigQTLDB. *Mamm Genome*. 2005;16(10):792–800.
69. Vilà C, Savolainen P, Maldonado JE, et al. Multiple and ancient origins of the domestic dog. *Science*. 1997;276(5319):1687–9.
70. Boyko AR, Quignon P, Li L, et al. A simple genetic architecture underlies morphological variation in dogs. *PLoS Biol*. 2010;8(8):e1000451.
71. Larson G, Piperno DR, Allaby RG, et al. Current perspectives and the future of domestication studies. *Proc Natl Acad Sci U S A*. 2014;111(17):6139–46.
72. Belyaev DK. Destabilizing selection as a factor of domestication. *J Hered*. 1979;70:301–8.
73. Hemmer H. Domestication: the decline of environmental appreciation. Cambridge University Press, Cambridge; 1990.
74. Schmutz S, Schmutz J. Heritability estimates of behaviors associated with hunting in dogs. *J Hered*. 1998;89(3):233–7.
75. Persson ME, Roth LS, Johnsson M, Wright D, Jensen P. Human-directed social behaviour in dogs shows significant heritability. *Genes Brain Behav*. 2015;14(4):337–44.
76. Kruska D. On the evolutionary significance of encephalization in some eutherian mammals: effects of adaptive radiation, domestication and feralization. *Brain Behav Evol*. 2005;65:73–108.
77. Gering E, Johnsson M, Willis P, Getty T, Wright D. Mixed-ancestry and admixture in Kauai's feral chickens: invasion of domestic genes into ancient Red Junglefowl reservoirs. *Mol Ecol*. 2015;24(9):2112–24.
78. Wilkins AS, Wrangham RW, Fitch WT. The "domestication syndrome" in mammals: a unified explanation based on neural crest cell behavior and genetics. *Genetics*. 2014;197(3):795–808.
79. Trut LN, Plyusnina I, Oskina I. An experiment on fox domestication and debatable issues of evolution of the dog. *Russ J Genet*. 2004;40(6):644–55.
80. Belyaev DK, Oskina IN, Trut N, Bazhan NM. The genetics and phenogenetics of hormonal characteristics of animals. 8. Analysis of corticosteroid adrenal-function variation in silver foxes under selection for domestication. *Genetika*. 1988;24(4):715–22.
81. Hare B, Plyusnina I, Ignacio N, et al. Social cognitive evolution in captive foxes is a correlated by-product of experimental domestication. *Curr Biol*. 2005;15(3):226–30.
82. Albert FW, Shchepina O, Winter C, et al. Phenotypic differences in behavior, physiology and neurochemistry between rats selected for tameness and for defensive aggression towards humans. *Horm Behav*. 2008;53(3):413–21.
83. Plyusnina I, Oskina I. Behavioral and adrenocortical responses to open-field test in rats selected for reduced aggressiveness toward humans. *Physiol Behav*. 1997;61(3):381–5.
84. Koinange EMK, Singh SP, Gepts P. Genetic control of the domestication syndrome in common bean. *Crop Sci*. 1996;36:1282–91.
85. Pérez-Vega E, Pañeda A, Rodríguez-Suárez C, Campa A, Giraldez R, Ferreira J. Mapping of QTLs for morpho-agronomic and seed quality traits in a RIL population of common bean (*Phaseolus vulgaris* L.). *Theor Appl Genet*. 2010;120(7):1367–80.
86. Doebley J, Stec A. Genetic analysis of the morphological differences between maize and teosinte. *Genetics*. 1991;129(1):285–95.
87. Doebley J, Stec A. Inheritance of the morphological differences between maize and teosinte: comparison of results for two F(2) populations. *Genetics*. 1993;134(2):559–70.
88. Burke JM, Tang S, Knapp SJ, Rieseberg LH. Genetic analysis of sunflower domestication. *Genetics*. 2002;161(3):1257–67.
89. Cai HW, Morishima H. QTL clusters reflect character associations in wild and cultivated rice. *Theor Appl Genet*. 2002;104(8):1217–28.

90. Poncet V, Lamy F, Enjalbert J, Joly H, Sarr A, Robert T. Genetic analysis of the domestication syndrome in pearl millet (*Pennisetum glaucum* L., *Poaceae*): inheritance of the major characters. *Heredity*. 1998;81(6):648–58.
91. Kukekova AV, Trut LN, Chase K, et al. Mapping loci for fox domestication: deconstruction/reconstruction of a behavioral phenotype. *Behav Genet*. 2011;41(4):593–606.
92. Darvasi A, Soller M. Advanced intercross lines, an experimental population for fine genetic-mapping. *Genetics*. 1995;141(3):1199–207.
93. Johnsson M, Rubin CJ, Höglund A, et al. The role of pleiotropy and linkage in genes affecting a sexual ornament and bone allocation in the chicken. *Mol Ecol*. 2014;23(9):2275–86.
94. Faris JD, Fellers JP, Brooks SA, Gill BS. A bacterial artificial chromosome contig spanning the major domestication locus Q in wheat and identification of a candidate gene. *Genetics*. 2003;164(1):311–21.
95. Simons KJ, Fellers JP, Trick HN, et al. Molecular characterization of the major wheat domestication gene Q. *Genetics*. 2006;172(1):547–55.
96. Clark RM, Linton E, Messing J, Doebley JF. Pattern of diversity in the genomic region near the maize domestication gene tb1. *Proc Natl Acad Sci U S A*. 2004;101(3):700–7.
97. Ji HS, Chu SH, Jiang W, et al. Characterization and mapping of a shattering mutant in rice that corresponds to a block of domestication genes. *Genetics*. 2006;173(2):995–1005.
98. Wright S. *Evolution and the Genetics of Populations*. Vol 1. Genetic and Biometrie Foundations. University of Chicago Press, Chicago; 1968.
99. Fisher RA. *The Genetical Theory of Natural Selection*. New York, NY: Dover; 1958.
100. Orr HA. Adaptation and the cost of complexity. *Evolution*. 2000;54(1):13–20.
101. Wagner GP, Kenney-Hunt JP, Pavlicev M, Peck JR, Waxman D, Cheverud JM. Pleiotropic scaling of gene effects and the 'cost of complexity'. *Nature*. 2008;452(7186):470–2.
102. Albert AY, Sawaya S, Vines TH, et al. The genetics of adaptive shape shift in stickleback pleiotropy and effect size. *Evolution*. 2007;62:76–85.
103. Wagner GP, Zhang J. The pleiotropic structure of the genotype-phenotype map: the evolvability of complex organisms. *Nat Rev Genet*. 2011;12(3):204–13.
104. Waddington CH. *The Strategy of the Genes*. London: Allen; 1957:86.
105. Breitling R, Li Y, Tesson BM, et al. Genetical genomics: spotlight on QTL hotspots. *PLoS Genet*. 2008;4(10):e1000232.
106. Fu J, Keurentjes JJ, Bouwmeester H, et al. System-wide molecular evidence for phenotypic buffering in *Arabidopsis*. *Nat Genet*. 2009;41(2):166–7.
107. Chesler EJ, Lu L, Shou S, et al. Complex trait analysis of gene expression uncovers polygenic and pleiotropic networks that modulate nervous system function. *Nat Genet*. 2005;37(3):233–42.
108. Heyne HO, Lautenschläger S, Nelson R, et al. Genetic influences on brain gene expression in rats selected for tameness and aggression. *Genetics*. 2014;198(3):1277–90.
109. Grant G. *Plant Speciation*. New York, NY: Columbia University Press; 1981.
110. Albert FW, Carlborg O, Plyusnina I, et al. Genetic architecture of tameness in a rat model of animal domestication. *Genetics*. 2009;182(2):541–54.
111. Lai Z, Kane NC, Zou Y, Rieseberg LH. Natural variation in gene expression between wild and weedy populations of *Helianthus annuus*. *Genetics*. 2008;179(4):1881–90.
112. Nätt D, Rubin CJ, Wright D, et al. Heritable genome-wide variation of gene expression and promoter methylation between wild and domesticated chickens. *BMC Genomics*. 2012;13(1):59.
113. Rubin CJ, Lindberg J, Fitzsimmons C, et al. Differential gene expression in femoral bone from red junglefowl and domestic chicken, differing for bone phenotypic traits. *BMC Genomics*. 2007;8(1):208.
114. Litvin O, Causton HC, Chen B-J, Pe'er D. Modularity and interactions in the genetics of gene expression. *Proc Natl Acad Sci U S A*. 2009;106(16):6441–6.
115. Ayroles JF, Carbone MA, Stone EA, et al. Systems genetics of complex traits in *Drosophila melanogaster*. *Nat Genet*. 2009;41(3):299–307.
116. D'Ennequin M. Plant domestication: a model for studying the selection of linkage. *J Evol Biol*. 1999;12(6):1138–47.
117. Monteiro A, Brakefield PM, French V. Butterfly eyespots: the genetics and development of the color rings. *Evolution*. 1997;51:1207–16.
118. Turner JR. Butterfly mimicry: the genetical evolution of an adaptation. *Evol Biol*. 1977;10:163–206.
119. Carlson BM. *Human Embryology and Developmental Biology*. 5th ed. Elsevier; 2014.
120. Trainor PA. Neural Crest Cells: Evolution, Development and Disease. Amsterdam: Academic Press; 2014.
121. Daetwyler HD, Capitan A, Pausch H, et al. Whole-genome sequencing of 234 bulls facilitates mapping of monogenic and complex traits in cattle. *Nat Genet*. 2014;46(8):858–65.
122. Hu J, Mungall C, Law A, et al. The ARKdb: genome databases for farmed and other animals. *Nucleic Acids Res*. 2001;29(1):106–10.
123. Wang J, He X, Ruan J, et al. ChickVD: a sequence variation database for the chicken genome. *Nucleic Acids Res*. 2005;33(suppl 1):D438–41.
124. Hu Z-L, Park CA, Wu X-L, Reecy JM. Animal QTLdb: an improved database tool for livestock animal QTL/association data dissemination in the post-genome era. *Nucleic Acids Res*. 2013;41(D1):D871–9.
125. Lim D, Cho YM, Lee KT, et al. The pig genome database (PiGenome): an integrated database for pig genome research. *Mamm Genome*. 2009;20(1):60–6.
126. Polineni P, Aragonda P, Xavier SR, Furuta R, Adelson DL. The bovine QTL viewer: a web accessible database of bovine quantitative trait loci. *BMC Bioinformatics*. 2006;7(1):283.
127. Ogorevc J, Kunej T, Razpet A, Dovc P. Database of cattle candidate genes and genetic markers for milk production and mastitis. *Anim Genet*. 2009;40(6):832–51.