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Molecular consequences of animal breeding

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The phenotypic diversity in domestic animals provides a unique opportunity to study genotype–phenotype relationships. The identification of causal mutations provides an insight into what types of mutations have contributed to phenotypic evolution in domestic animals. Whole genome sequencing has revealed that fixation of null alleles that inactivate genes, which are essential under natural conditions but disadvantageous on the farm, has not been a common mechanism for genetic adaptation in domestic animals. Numerous examples have been revealed where structural changes cause specific phenotypic effects by altering transcriptional regulation. An emerging feature is also the evolution of alleles by the accumulation of several consecutive mutations which affect gene function.

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Introduction

Domestic animals constitute a resource for biological research due to the remarkable phenotypic changes that have occurred since domestication. There are several mechanisms that have contributed to this evolution.

(i) *Directional selection for adaptive mutations*. These make the animals better adapted for human purposes. For a long time this was based on phenotypic selection, where humans kept animals with favourable phenotypes for breeding. After the development of the theory of quantitative genetics more and more sophisticated statistical procedures have been developed to select animals with outstanding estimated breeding values. This has led to a remarkable improvement in animal production during the last 50 years.

(ii) *Directional selection for phenotypic appearance — fancy breeding*. Not all the traits that have been selected in domestic animals are adaptive. Apparently humans have a strong preference for phenotypic diversity among our domestic animals. For all domestic animals, humans have selected mutants which cause appealing phenotypic appearance as long as this appearance does not interfere with the utility of the animals. This is an important reason why we have black pigs with white belts or dogs with dorsal hair ridges. For those domestic animals that are used as pets a broad range of mutations is tolerated. This is probably the main reason why dogs show such an extensive phenotypic diversity [1].

(iii) *Natural selection*. Throughout the history of animal domestication natural selection has been operating in parallel with human selection. Genetic variants which promote survival or reproductive output in the new environment created by humans have been favoured by natural selection.

(iv) *Genetic drift*. It is also anticipated that some of the traits have been altered simply by genetic drift due to relaxed purifying selection in the farm environment. It is possible that this has contributed to the rich diversity of coat and plumage colour in domestic animals, although selection for coat colour variants also can be adaptive by facilitating animal husbandry as well as being favoured by fancy breeding [2].

Mutations with large favourable effects have been under strong positive selection in domestic animals and the same exact mutation is often found in different breeds all over the world, in sharp contrast to the extreme allelic heterogeneity often underlying inherited disorders in humans. This is particularly common for novel gain-of-function or dominant-negative mutations, because such mutations often represent a rare event. Throughout the history of animal domestication, human trades have efficiently spread favourable mutations around the world. Examples of widespread mutations are a nonsense mutation in *DMRT3* causing the ability to perform alternate gaits in horses [3••] and an *FGF4* retrogene associated with short legs in dogs [4••]. In both these cases the same mutation on the same haplotypic background is present across many breeds. This situation facilitates the identification of causal mutations underlying phenotypic traits, because haplotype sharing across breeds can be used to fine map the mutation and the phenotypic effect of a mutation can be investigated on different genetic backgrounds. However, exceptions to this rule occur and then it is often when there is selection for a loss-of-function allele, as a gene can be inactivated in many

ways. A prominent example of this is that selection for muscle growth in beef cattle has resulted in an allelic series disrupting *myostatin* (*MSTN*) function; MSTN acts as a suppressor for muscle growth [5].

The aim of this paper is to review what we have learnt from the molecular characterization of loci underlying phenotypic variation in domestic animals. The main focus is on monogenic traits, since it is still challenging to reveal causal mutations which underlie multifactorial traits. The focus is on traits rather than inherited disorders, because what we can learn from deleterious mutations under purifying selection in domestic animals is not fundamentally different from what we can learn from the much more extensive literature on human disorders, whereas the rapid evolution of phenotypic traits in domestic animals provides a unique opportunity to gain insight into genotype–phenotype relationships.

Is less more?

Olson [6] proposed that loss of gene function may be an important mechanism for rapid genetic adaptation to a new environment in natural populations as well as in domesticated plants and animals. The argument is that genetic mechanisms which control for instance behaviour, reproduction or growth that are of crucial importance for adaptation under natural conditions may be disadvantageous in the farm environment. One example when less is more is homozygosity for null alleles at the *myostatin* locus in beef cattle that releases repression of muscle growth [5], and another is the disruption of a repressor binding site in intron 3 of *IGF2* that leads to increased muscle growth in pigs [7••]. We have carefully searched for the presence of such inactivating mutations in coding sequences by using whole genome resequencing of pooled samples which represent different populations of chickens [8•] and pigs [9•]. These screens did not reveal a single example of a null allele in a well-conserved, single copy gene which occurs at a high frequency in any of the populations studied. False negatives may occur in these screens because both the chicken and pig genome assemblies are not finished assemblies, which means that we may have failed to detect inactivating mutations because the gene model was incorrect or incomplete. Nevertheless, we conclude that fixation of null alleles has not been a common mechanism for phenotypic evolution in domestic animals.

Structural changes mediate phenotypic changes by altering transcriptional regulation

Structural changes have played a prominent and important role for phenotypic evolution in domestic animals (Table 1). Duplications appear as the most common structural variant associated with phenotypes followed by deletions, inversions and translocations, and there is one example of an expressed *FGF4* retrogene causing chondrodysplasia in dogs [4••]. A common theme for these structural changes is that they lead to an altered

Table 1

Examples of structural variants associated with phenotypic traits in domestic animals

Species	Trait	Mutation	Gene(s)
Cattle	Colour sidedness	492 kb translocation[a]	*KIT* [31••]
Chicken	Pea-comb	Copy number expansion[b]	*SOX5* [14]
	Rose-comb	7.4 Mb inversion[a]	*MNR2* [15•]
	Dark brown colour	8.3 kb deletion	*SOX10* [32]
	Naked neck	~70 kb translocation	*BMP12* [33••]
	Fibromelanosis	Complex[c]	*EDN3* [34]
Dog	Hair ridge	133 kb duplication	*FGF3*, *FGF4*, *FGF18*, *ORAOV1* [35]
	Chondrodysplasia	Retrogene insertion	*FGF4* [4••]
	Wrinkles[d]	16.1 kb duplication[d]	*HAS2* [36]
	Amylase activity	~8 kb duplication	*AMY2B* [37•]
Goat	Polled[e]	11.7 kb deletion	*PISRT1*, *FOXL2* [38]
Horse	Greying with age[f]	4.6 kb duplication	*STX17*, *NR4A3* [39,40•,41]
	Tobiano white spotting	~40 Mb inversion	*KIT* [42]
Pig	Dominant white colour	Several duplications	*KIT* [9•,43,44]
Sheep	White colour	190 kb duplication	*ASIP*, *AHCY* [45]

[a] Two alleles identified (see Table 2).
[b] Massive expansion of a duplicated sequence.
[c] The mutation is a complex rearrangement where two fragments, 129 kb and 172 kb in size and located 417 kb apart on the wild-type version of chicken chromosome 20, are both duplicated. In addition, the duplicated copy of the 172 kb fragment is inserted between the two copies of the 129 kb fragment but in an inverted orientation!
[d] This mutation also predisposes to Familial Shar-Pei Fever — a periodic fever syndrome. The duplication shows a copy number expansion.
[e] Lack of horn, also associated with intersexuality in males.
[f] This mutation also predisposes to melanoma development.