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NEWS AND COMMENTARY

Domestication: a long-term genetic experiment

Domesticated species form a treasure-trove for molecular characterization of Mendelian traits by exploiting the specific genetic structure of these species in across-breed genome wide association studies

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Domesticated species have been important models for understanding phenotypic consequences of selection and genetics in the past 150 years. Among the most famous examples, is the work by Charles Darwin on the breeding of fancy pigeons that formed one of the pillars of his theory of evolution. Unknown to Darwin, around the time of publication of 'On the Origin of Species', Gregor Mendel conducted experiments on domesticated pea plants that would form the basis of the science of genetics. Domesticated animals and plants basically constitute the kinds of long-term genetic experiments researchers usually can only dream about. In fact, domestication and selection for specific phenotypes have resulted in thousands of generations of human-mediated selection and change, bringing about countless distinct phenotypes.

Today, the same rationale for applying domesticated species to fundamental questions in genetics still applies. Over the past 2 decades, numerous specific, often experimental, crosses have been used for the mapping and subsequent identification of the genes for a variety of phenotypes in domesticated species (see review by Andersson and Georges, 2004). Although successful in specific cases, the mapping resolution generally was low and the success very much depended on the existence of known mutants in other species with similar phenotypes, in particular the mouse. As a result, the number of Mendelian traits in domestic animals for which the molecular mechanism is known is limited (Online Mendelian Inheritance in Animals (OMIA): http://www.ncbi.nlm.nih.gov/omia).

Phenotypes shared between domesticated populations very often turn out to have a shared genetic basis, that is, the same underlying haplotype is responsible for the shared phenotypic trait. Such 'founder phenotypes' caused by *de novo* mutations that occurred a long time ago in wild or domesticated populations were selected for different breeds. As breeds often have been around for hundreds of generations or more, linkage disequilibrium between the trait locus and adjacent genomic regions has been broken down considerably. The independent selection for the same phenotypes caused by the same mutation in a variety of breeds, separated by a large number of generations, has made domesticated species a treasure trove for the identification of the genes underlying many of these phenotypes.

High-density single-nucleotide polymorphism (SNP) assays that are currently available for many domesticated species are paving the way for efficient and cheap genome-wide characterization of variation across a wide range of domesticated and wild forms. This allows the direct exploitation of the specific genetic structure of domesticated species. At the present time, this approach has been most extensively used in the dog, aided by the vast number of breeds and distinct phenotypes that are available. It has been suggested that the dog, because many of its phenotypes have discrete qualitative modes of inheritance, represents a special case (Shearin and Ostrander, 2010a, b), although that view was recently challenged in a commentary published in this journal (Hedrick and Andersson, 2011). With 566 entries, dog is clearly the domesticated animal species with the largest number of entries in the OMIA catalogue (Lenffer *et al.*, 2006), even though only 66 of these have underlying genes identified. The extraordinary power of across-breed genome-wide associatiom study was demonstrated in a recent study by Vaysse *et al.* (2011) determining candidates for genes underlying behavioral traits, ear and tail morphology, and confirming the association with body size for the *IGF1* gene, across no less than 46 dog breeds.

The study by Wragg *et al.* (2012) in this issue of *Heredity*, now extends this approach to chicken. Of all domesticated birds, the chicken is the only species with a sizeable number of entries in OMIA (188) and, as in dogs, the underlying causative gene has been identified for only a small number of traits (32). Many different breeds and phenotypes have been identified in chicken, more than in any other domesticated bird species and, in addition, it is the only bird species for which a high-density genotyping assay with around 55 000 SNPs is currently available (Groenen *et al.*, 2011). Using this SNP-genotyping assay for an across breed association study, Wragg *et al.* (2012) reveal or confirm several loci and genes involved in earlobe, skin and egg pigmentation and in comb shape (Figure 1). Maybe the most important aspect of their paper is the fact that they were able to do so using only a very limited number of animals, clearly emphasizing the power of this approach. The key to this power lies in the use of very different backgrounds, highlighting the fact that even in a very diverse species

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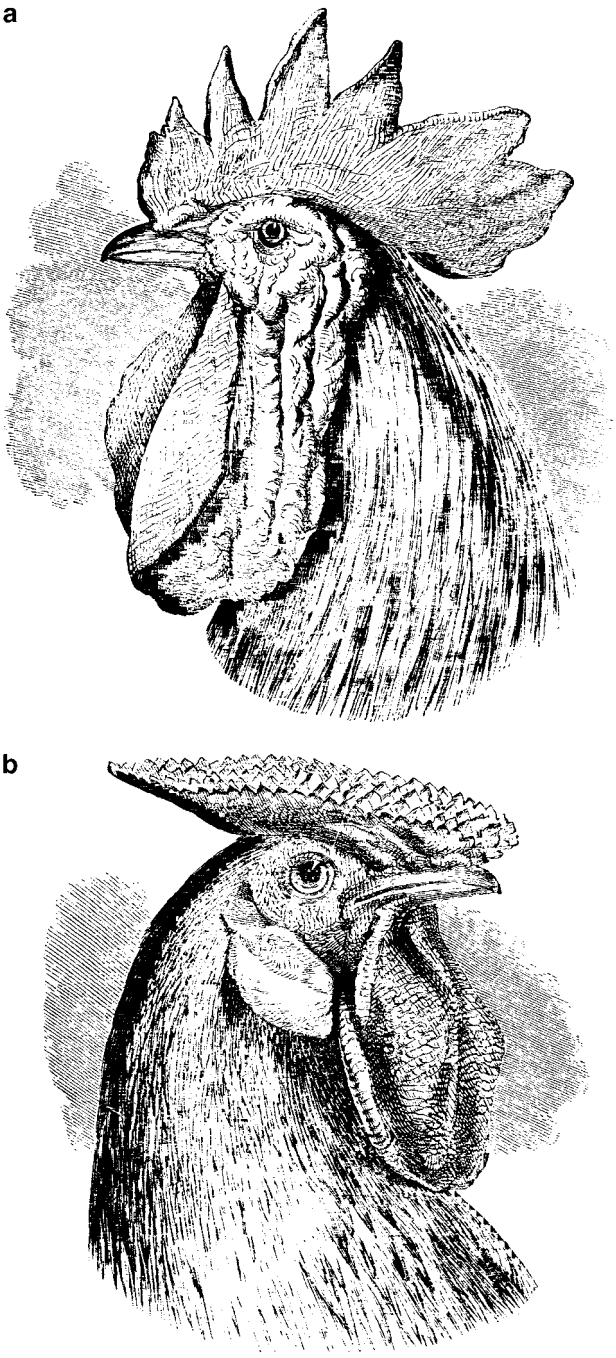

Figure 1 Spanish fowl (**a**) and Hamburgh (**b**) fowl. Both of these breeds feature in Wragg *et al.* (2012) to elucidate the genetic basis of white earlobe (Spanish and Hamburgh), and rosecomb (Hamburgh). These pictures are Figures 30 and 31, respectively, from the first edition (1868), of Charles Darwin's 'The Variation of Animals and Plants Under Domestication', highlighting that these breeds, then and now, yield important insights into phenotypic consequences of selection and genetics.

such as chicken, many of the Mendelian traits may share a common origin. It also shows that, although linkage disequilibrium (LD) in many breeds may extend to shorter physical distances compared with mammalian breeds and with little overlap in haplotype block structure, across-breed mapping is a valuable tool for chicken as well.

What these results in the dog and chicken show is that domesticated species form a treasure-trove for efficient molecular characterization of Mendelian traits. Across-breed association analysis, however, can be extended to production traits that are much more quantitative in nature. Such traits have been difficult to tackle using classical linkage studies. A fine example of a domesticated species where an across-breed association study has been applied is cattle. Exhaustive databases for milk and other production traits that exist for Holstein–Frisian and other breeds are put to maximum use this way. For instance, Hayes *et al.* (2009) applied an association analysis to find genes responsible for adaptation in milk production to local climate. While the study was able to find associations in a Frisian–Holstein population, the associated haplotypes, for two loci, were extremely large because of the extensive LD in this breed. Validating the association with another breed, making use of the low LD between breeds, associated regions shrank to a size where candidate genes could be identified.

Across-breed mapping studies that have been published so far mark only the beginning of mining the information on phenotype-altering variation harbored in domesticated breeds. As more exhaustive collections of phenotypic data for many different breeds become available, the current set of tools to characterize genetic variation can be applied to elucidate the journey of haplotypes through space and time that confer the associated function.

Still, tracking these haplotypes, broken down by thousands of generations since domestication, requires a highly detailed characterization of genomic variation. Exactly, the fact that haplotypes were broken down allows for the fine-mapping characteristics that make across-breed association feasible, but the high-density genotyping tools of today may not be dense enough. Wragg *et al.* (2012) estimate that for chicken the density should be at least around 100 000 SNPs, two-fold higher than the assay they used. Although higher density SNP chips have recently been developed (D Burt, personal communication), it is to be expected that, in particular, next-generation sequence analysis will contribute greatly in the years to come. With more detailed tracking of haplotypes that are identical by descent, investigating phenotypic similarities across divergent populations will become even more powerful. With both high-density genotyping and next generation sequencing revolutions in full swing in many domesticated species, we can now truly begin to realize the vision of Darwin and Mendel by fully mining the phenotypic and genotypic variation in this great experiment of humanity that we call domestication.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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