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A Genomics Perspective on Pig Domestication

Mirte Bosse

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Abstract

Land animal domestication has typically led to remarkable phenotypic diversity, stemming from a broad genetic background. The process of land animal domestication turns out to be a complex, long-term event with extensive gene-flow between wild and captive populations. Using pig as model, this chapter provides an in-depth overview of domestication-related events leading towards the genetic diversity in extant pig breeds. Five events in the evolutionary history and domestication of pigs can be recognized that are important for the genetic variation in modern pig genomes: (1) Speciation of *Sus* species in Island South-East Asia (ISEA); (2) Divergence between European and Asian lineages; (3) Independent domestication leading to separate domesticated clades in Europe and Asia; (4) Hybridization between domesticated pigs from Asia and Europe; and (5) Breed formation. Remarkably, the extensive mixture of genetic material leading towards the current European commercial pigs has resulted in domestic breeds that are genetically more diverse than their wild ancestors. Nowadays, commercial breeding and genomics go hand in hand. Genomics has not only proven useful to provide understanding about the domestication history of pigs but also about the molecular mechanisms underlying traits of interest. Moreover, genomic selection is an important tool integral to modern commercial breeding.

Keywords: genomics, pig, hybridization, selection, domestication

1. The process of livestock domestication

Domestication of land animals has typically led to a wide variety of domestic forms, with remarkable phenotypic diversity not seen in the wild. However, the underlying molecular variation resulting in a specific phenotype often stems from mutations predating domestication. Although domestication generally leads towards a reduction in effective population size, land animal domestication cannot be seen as a simple split of a subset of individuals from

their wild progenitors. The meaning of the word domestication is poorly defined and lacks consistency across different scientific disciplines [1]. From a population genetics perspective, domestication results in a deliberate separation of the captive, and then domesticated population from its parent population. Domestication is, therefore, initially indistinguishable from any other event that results in reduction of gene-flow between populations, and creating opportunity to respond to new selective pressures [2]. The simplest definition of domestication considers a domestic population as a subset of the wild population with cessation of gene-flow [3]. Therefore, one can expect that domestication results in a reduction of genetic variation in the domesticated population. The onset of domestication occurred in multiple geographically distinct areas during the late Pleistocene to early Holocene transition (12,000–8200 B.P., [4]). The process of land animal domestication, however, turns out to be a complex, long-term event initiated by cultural transitions related to food production [5, 6]. The definition of an animal to be considered domesticated varies, however, some common characteristics emerge from literature. Teletchea and Fontaine propose that a domesticated animal should be selectively bred in captivity and modified from its wild ancestors [7]. It is important to realize that those early considered domestic populations were genetically and phenotypically hardly distinguishable from wild types, and therefore geographical location was a better predictor of local characteristics than domestication status [3]. The general assumption that multiple centers of domestication exist has important implications for the source of genetic and phenotypic variation in domesticated species. In cattle, for example, two distinct cattle lineages that separated ~300,000 ya, contributed to two major lineages of extant cattle, that is, taurine cattle (originating from *Bos taurus*) and indicine cattle (originating from *Bos indicus*) [8]. It is not unlikely that multiple populations of wild land animals that are now extinct contributed to the genetic diversity that is observed in modern breeds [9]. The domestic animal populations accompanying human settlements did not necessarily remain at their original location of domestication. Rather, they moved along with early farmers spreading in Asia and from Eastern Anatolia throughout Europe [10]. During this process, the connection of domestic animals and farmers was relatively loose, enabling animals to hybridize with local wild populations [11]. Only centuries later, animals were actually kept in strict enclosures and intentionally bred for specific purposes, leading towards the best-known characteristic of domestic animals: docility [12]. This controlled environment drastically reduced the opportunity of domestic herds to interbreed with local wild populations, which enabled strong divergence between domestic and wild forms. We should realize the genetic basis of the modifications leading towards morphological differences in domestic animals compared to their wild ancestors is mostly provided by standing genetic variation, that is, mutations that were already present before the onset of domestication and selection. Therefore, indicating the genetic underpinnings of domestication remain challenging [13, 14]. Arguably, we can speak about a domestic population if not only the gene pool is distinct from the wild variety, but also (artificially) selected variants leading to desired phenotypes are at high(er) frequency in the domestic population [15–18]. In this chapter, an in-depth overview is provided for the complex process of domestication, admixture, and selection leading towards the genetic diversity in extant breeds, using pig as model.

2. Genomic insight in pig domestication

Domesticated species are good models to study genomic and phenotypic consequences of demography and selection [19]. The use of higher DNA marker densities has enabled researchers to reveal the complexity of livestock domestication, which was shown to be far more complex than a single sampling from the wild [20]. Genotyping and sequencing technologies have opened up many opportunities to reveal the complex history of domestication, admixture, and selection in livestock [4, 20]. Combining modern sequence technologies with extensive studies on fossil records and land animal usage now enables the reconstruction of domestication in details. Apart from a suitable history and documentation, the availability of detailed genetic information is crucial to be able to study genomic alterations due to domestication. Pig (*Sus scrofa*, Linnaeus, 1758) was the first livestock species for which a genome consortium was established with the intention to completely map the genome [21, 22]. The design of a 60k single nucleotide polymorphism (SNP) chip for pigs in 2009 greatly contributed to the applicability of genomics techniques in pig breeding, and simultaneously increased possibilities for population genomics studies [23]. The establishment of a consortium to sequence the pig genome in 2003 and publication of the pig reference genome in 2012 opened up an even greater window of opportunities to study various aspects of the genetics of pig, since the highest resolution possible became reality [21, 24]. Together with the evolutionary history of pig, these provide an unprecedented study system to demonstrate the impact of domestication from a genomics perspective. Pig genomes contain a complex composition of segments, reflecting the different backgrounds that contributed to the domestic animal it is today. Disentangling these genomic signatures provides enormous information about the complex background and history of the worlds' most consumed meat type [25].

3. Conceptual history of the pig (*Sus scrofa*)

Here I will discuss genomic variation within and between different populations of pigs, providing deeper understanding of how domestication has influenced genetic diversity of pigs. Five major events in the evolutionary history and domestication of pigs can be recognized that are of importance for the distribution of genetic variation in modern pig genomes (**Figure 1**).

3.1. Speciation of *Sus* in island South-East Asia

Knowledge about the source of the domesticated form, the origin of the species, is essential to understand genetic variation within modern breeds. The Suidae family is particularly interesting for molecular genetic studies as it is one of the few mammalian lineages that has closely related species living today. Multiple *Sus* species originated roughly ~4 million years ago on Island Southeast Asia (ISEA). The island structure in this region probably promoted speciation, since the bearded pig *Sus barbatus*, the warty pigs *S. celebensis* and *S. verrucosus* but also wild *S. scrofa* occur on separate islands. The phylogenetic structure within the genus *Sus*

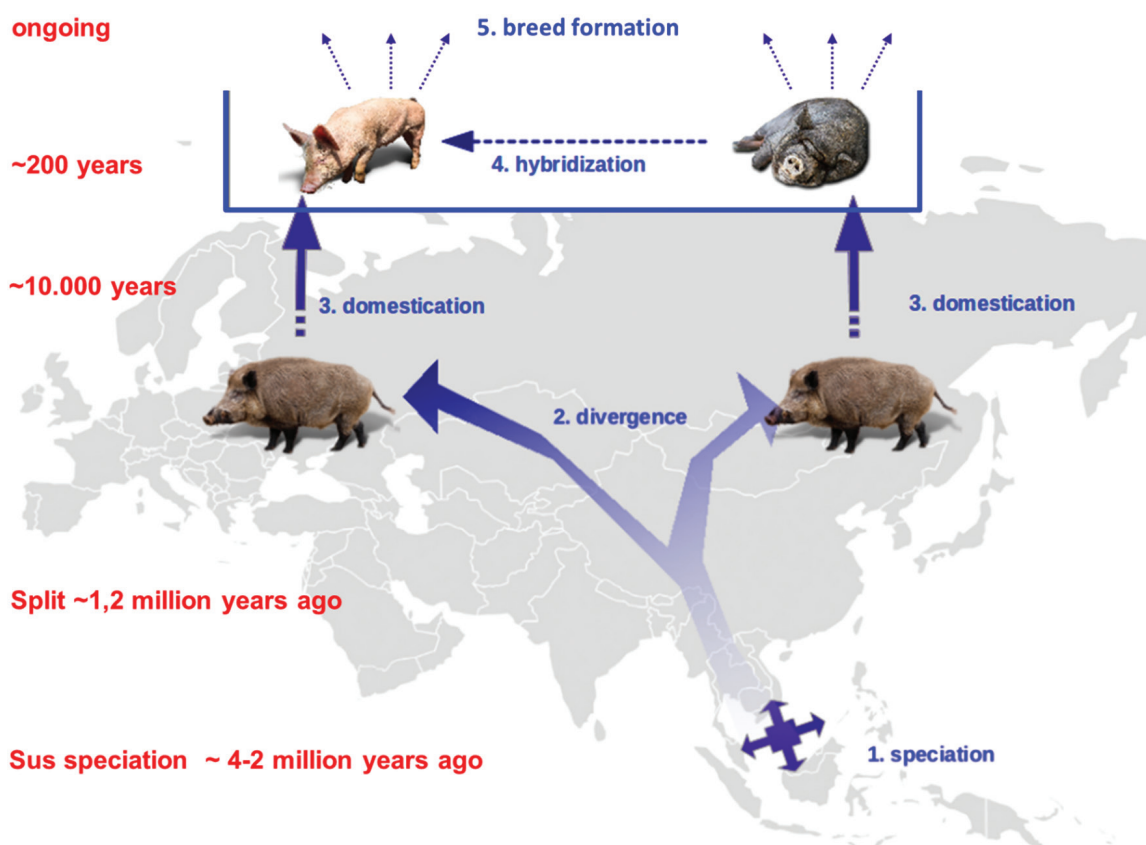


Figure 1. Schematic overview of the history of the pig (*Sus scrofa*). Five main events in pig history are indicated in blue, with the approximate timing of those events in red: (1) Speciation of *Sus* species in Island South-East Asia (ISEA). (2) Divergence between European and Asian *S. scrofa* lineages. (3) Independent domestication leading to separate domesticated clades in Europe and Asia. (4) Hybridization between domesticated pigs from Asia and Europe. (5) Breed formation.

has been studied intensively and revealed a complex history of admixture [26, 27]. The past connection of landmasses at the Sunda shelf and isolation of Indonesian islands by the rapid sea level rise after the last glaciatiion period [28] created a dynamic process of (re)colonization, isolation and admixture of different *Sus* species and populations [29, 30]. The species that gave rise to the domesticated pig, *Sus scrofa*, has its origin in Southeast Asia some ~4 Mya and colonized almost the entire Eurasian mainland from there. The widespread and opportunistic nature of this species probably contributed to the fact that *Sus scrofa* is the only pig species that was successfully domesticated [25].

3.2. Divergence between European and Asian *S. scrofa*

Sus scrofa is widespread within Eurasia (**Figure 1**) and consists of many isolated wild and domesticated populations. The divergence between Western-European and Eastern-Asian populations has been estimated at about 1.2 Mya [24, 29], and has resulted in many fixed molecular differences between the two groups. This divergence not only resulted in a European and an Asian *S. scrofa* clade, but also in differences in demographic history and population size. The last glacial maximum probably reduced population sizes of both European and Asian

wild boars, but the reduction was most severe in Europe [24]. The geographic distribution of wild boar over Europe faced another severe decline starting in the middle ages and lasted until the late eighteenth century [25]. In the mid-nineteenth century, natural or human-mediated recolonization events resulted in isolated populations expanding their range. Some of these isolated populations were small in effective size for decades or longer, causing inbreeding and population differentiation. Local re-stocking of populations with geographically distinct wild boar resulted in complex genetic structures and signatures of population dynamics [31, 32]. Such complex genetic architectures have been detected in Italian and Luxembourgian wild boars. However, these mixed genomes could have been shaped due to ancient glaciation events [33] or because of recent mixture [34]. Asian *Sus scrofa* is thought to have had a larger effective population size which, together with its proximity to the origin of the species, results in higher genetic diversity compared to the European clade [24, 35, 36]. These highly distinct groups of wild boar provided the basis of the genetic background of the later domesticated pigs.

3.3. Independent domestication leading to separate clades

The demographic and geographic history of the domesticated pig may be just as complex as that of its wild counterpart. There is compelling evidence that pig domestication events occurred at multiple locations, Eastern Anatolia and China independently, some 9000–10,000 years ago [26, 37]. Domestication has not been a single event, but rather a long period with recurrent admixture with wild populations [38]. Following initial domestication, the traits selected as well as how animals were kept, strongly differed in Europe and Asia resulting in highly different domesticated pigs between Europe and Asia. Asian pigs were kept in close proximity of humans, often integrated in their settlements. By contrast, European pigs were roaming freely in forested areas in the surroundings [39, 40]. Only during the Industrial Revolution, a more strict pig farming system was adopted and implemented to fulfill the increasing demand for pork. Because of recurrent gene-flow between wild and domestic pigs, a reduction in genetic diversity cannot be observed in domesticated pigs compared to their presumed wild counterparts [35, 38, 41]. One should realize though that European and Asian domesticated pigs have been geographically isolated for over a million years ago, because they have distinct wild origins. Therefore, they genetically resemble local wild boar more than domestic pigs from different geographic origins [24, 35]. This dichotomy also underlies the fact that European pigs and wild boar are genetically less diverse than Asian wild boar and domestic pigs.

3.4. Hybridization between domesticated pigs of different origin

It is well documented that during the Industrial Revolution in Europe, European pigs have been deliberately hybridized with Asian pigs. Urbanization in Europe increased the demand for meat such as pork, but during those times, pig farmers would still have their pigs roaming in surrounding forests. Forest cover was decreasing and a different pig production system seemed inevitable [40]. Due to this changing environment, pig breeders sought a way to improve their stock in such way that pigs had to become adapted to living in small(er) enclosures, be more prolific and gain weight more rapidly. This led to selection for traits better adapted to

the changed environment. Many of these traits were already present in Asian domestic pigs. Therefore, British farmers started crossbreeding their own pigs with these Asian pigs [40]. This introgression of Asian genetic material into European populations has long been demonstrated by genetic markers [42, 43]. Moreover, the intentional crossbreeding and consecutive artificial selection on Asia-derived traits enabled adaptive loci to emerge in the genome of European domestic pigs. Genes of Asian origin have been demonstrated to contribute to increased fertility and fatness in commercial Large White pigs [44, 45]. Very recently, hybridization between wild and domesticated pigs has been reported in Western Europe, resulting in traceable Asian genetic material in local wild boar populations in Germany [31, 32, 34].

3.5. Breed formation and globalization

Due to the worldwide consumption of pork, the species is farmed at a global scale, far exceeding its original natural distribution (IUCN). The influence and contribution of commercial pig breeds to local ecology and biodiversity is however debated [31, 32, 46]. Also, escape or intentional release of local stocks have resulted in feralization of domesticated pigs, which is now a major population in the United States, although the continent is not part of the native range of the species [47]. The domesticated pig as it is used nowadays for agricultural purposes consists of many breeds that have been separated and kept isolated for decades, which has resulted in many genetic differences between these breeds. Breed and population specific genetic studies have greatly enhanced the dissection of complex traits that are economically important. Knowing and understanding the origin and distribution of variation in (domesticated) species is important for conservation of genetic resources, such as culturally important heritage breeds [48]. Local husbandry and breeding techniques have created an enormous diversification of pig breeds. Generally, European breeds can be categorized into global commercial breeds, stemming from the White type in England, and local heritage breeds, developed locally and now often endangered [39]. It is notable that many heritage breeds genetically resemble the local wild boar more than global pig breeds, most likely because they were not improved by Asian gene-flow two centuries ago [35, 49–51]. The globalization of pig breeding and consumption has swamped local pig breeds with common commercial breeds from British heritage background, such as Large White, Landrace, Pietrain and Duroc [39]. Also, extensive admixture between breeds of different origin is known to occur, highly dependent on local breeding practices.

4. The hybrid nature of (pig) genomes

Increasing evidence showed that humans play an important role in stimulating hybridization in wild species, either unintentionally or on purpose. Human-induced hybridization can not only be a by-product of globalization as some species became widely distributed due to human mobility, but it can also be intentional such as in domesticated species [40, 52]. It is becoming apparent that many livestock species/breeds are actually a mixture of highly divergent populations with a mixed demographic history, combined in one genome. The formation of livestock breeds provides a good example of how man has influenced the

genomic architecture of a species. In cattle, for example, exchange of genetic material between different species promoted the uptake of beneficial traits from closely related species [53]. In pig, domestication does not seem to have left a clear population bottleneck, as demonstrated by the high level of genetic variation in European pigs [38]. This suggests that the majority of the genetic variation that is present in European wild boar is also present in domestic breeds, even though modern pigs are phenotypically clearly different from their wild counterparts. Moreover, the gene-flow with wild populations as well as between different domestic lineages enabled pig breeders to select for locally and globally preferred traits, using a broad genetic background [44, 45]. Remarkably, the extensive mixture of genetic material leading towards the current European commercial pigs has resulted in domestic breeds that are genetically more diverse than their wild ancestors in Europe [24, 35, 36, 41]. This counter-intuitive characteristic of commercial pigs is mainly driven by the influx of Asian genes during the Industrial Revolution [45]; local heritage breeds that do not display signs of Asian gene-flow tend to have lower genetic diversity [50, 51]. Nowadays, many breeds and definitions are used to describe the origin of (local) stock, with some being a complex mixture of Asian and European heritage, depending on the geographical region and the breeding practice of pig farmers.

5. Breeding and genomics go hand in hand

Pig farming has drastically changed since first domestication. Today's elaborate pig breeding industry has only few characteristics in common with early pig farmers, and has resulted in a highly professional large-scale pork production system, making use of latest technologies in animal breeding. Selection for particular traits not only improved due to more precise phenotyping and better defined traits such as carcass quality, growth rate and fertility [54], but also because of crossing breeds with desirable traits of different origins [45]. The use of pedigree information and large-scale tracking of animal relatedness has speeded up the improvement of pig breeds. In other livestock, especially cattle, the implementation of the use of genetic markers on top of pedigree information resulted in even more efficient selection [55]. The recent and rapid genetic progress can be achieved due to the implementation of genomic selection, in which animals are selected based on their performance predicted from their genotypes, rather than phenotypes [56]. This way, animals can be selected at an earlier stage, and predicted phenotypes for typically female traits can also be implemented using genotype information from males [57, 58].

Genomics has not only proven useful as a tool in genomic selection, but also has provided more understanding about the molecular mechanisms that underlie traits of interest. Knowledge about the link between genes and trait enables more accurate breeding [54]. Moreover, if the function of a specific gene is known, it can provide insight into the selection history of a breed. Numerous studies have successfully identified selection for genes linked to specific commercially important traits (**Table 1**). Interestingly, some of these genes under selection in European breeds have an Asian origin [59–61]. Also, genome-wide scans for detrimental variants have identified mutations in commercial populations with negative effects [62, 63].

Gene	Trait	Study
<i>KIT</i>	Coat color	Andersson and Plastow [66]
<i>KITLG</i>	Coat color	Okumura et al., [61]
<i>MC1R</i>	Coat color	Kijas et al., [67]; Fang et al., [68]
<i>EDNRB</i>	Coat color	Ai et al., [59]; Wilkinson et al., [69]
<i>IGF2</i>	Lean growth	van Laere et al., [70]
<i>RYR1</i>	Lean growth	Fujii et al., [71]
<i>PRKAG3</i>	Lean growth	Milan et al., [72]
<i>NR6A1</i>	Body size	Rubin et al., [73]
<i>PLAG1</i>	Body size	Rubin et al., [73]
<i>LCORL</i>	Body size	Rubin et al., [73]
<i>OSTN</i>	Body composition	Rubin et al., [73]
<i>CLDN1</i>	Fertility	Choi et al., [74]
<i>AHR</i>	Fertility	Bosse et al., [44]
<i>TWIST1</i>	Fatness	Choi et al., [74]
<i>LEMD3</i>	Ear morphology	Wilkinson et al., [59]

Table 1. Non-exhaustive list of genes associated with commercially important traits in pigs.

Recent work demonstrates that some variants that cause lethality in homozygous state are present at relatively high frequency in commercial pig lines [64, 65]. Knowing these recessive lethal mutations can aid in avoiding matings between carriers of such mutations within the breeding scheme. Overall, genomics has provided valuable insight into variation in pigs: what its origin is, how is it maintained, reduced and increased. This turned out to be a complex interplay of molecular processes, selection, demographic history, gene-flow and human interference. Moreover, genomics is an important tool in the pig industry nowadays and is integral to modern commercial breeding.

Author details

Mirte Bosse^{1,2*}

*Address all correspondence to: mirte.bosse@wur.nl

1 Wageningen University & Research – Animal Breeding and Genomics, Wageningen, The Netherlands

2 VU University Amsterdam – Animal Ecology, Amsterdam, The Netherlands

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