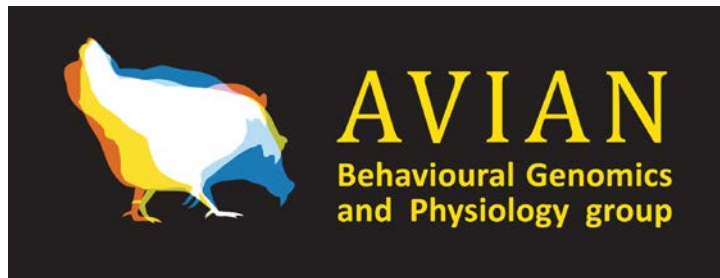


The genetic determinants of fear and stress in domesticated animals

Introductory essay, 2012

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1 Abstract

Genes, environment and the interaction between them shape behaviour. Various model animals have been used to find the genes that underlie behaviour. Domesticated animals have been proven to be useful in deciphering the genetic basis of complex behaviour such as anxiety and aggression. This review discusses the genes that affect behaviour and the environmental factors that modify behaviour by regulating gene expression and brain function. The genetic basis of quantitative traits such as anxiety and the contribution of domestication experiments in decoding them will be the focus. At the end, our present knowledge about cherry-picked genes during domestication and their pleiotropic effect on animal welfare and health will be covered. Both humans and domesticated animals suffer from novel stressors as they adapt a new lifestyle. Finding the genes and mechanism which are involved in modulating the stress response in animals can help us both in improving animal welfare and to understand the identity of stress related psychological disorders in humans.

2 Introduction

Organisms perceive stimuli via their sensory organs, based on their internal motivation and prior experiences they interpret them, and then a visible motor pattern occurs which is called behaviour. In other words behaviour can be defined as all visible actions of the animals and might be simple such as a reflex or a complex behavioural pattern ([Bendesky and Bargmann, 2011](#)). Genes regulate development of sensory organs, sensory and motor neural systems, and muscular system, thus ultimately they play a fundamental role in shaping behaviour. ([Jensen, 2006](#)).

The definition of the term “stress” is the subject of scientific debate, and the situations ranging from a slightly challenging stimulus to extremely aversive conditions are termed stress in various publications ([Koolhaas et al., 2011](#)). [McEwen \(2000\)](#) represented the term: “Stress may be defined as a real or interpreted threat to the physiological or psychological integrity of an individual that results in physiological and/or behavioral responses.” Naturally, the stress response can be adaptive by participating in allostasis (the process where an organism dynamically adapts to unpredictable or predictable events, or in other words, maintaining stability through changes) ([McEwen and Wingfield, 2003](#); [Korte et al., 2005](#)). But chronic or repeated environmental challenges such as social conflicts or changes in life condition may lead to pathologically deleterious and sometimes irreversible changes in the physiology and behaviour of the organisms ([McEwen, 1993](#)). An example of these radical changes in life condition can be seen in the captive animals, where they live in a vastly different situation in comparison to the wild animals, thus they are exposed to various novel stressors ([Rauw et al., 1998](#)). Individuals show different stress response to the novel stressors caused by the drastic change of their life condition in captivity. Like other physiological and behavioural characteristics, stress response is also influenced or even pre-determined by genes ([Jensen, 2006](#); [Albert et al., 2009](#)).

Some animal species have undergone a morphological, physiological and behavioural adaptation process called domestication, where they have adapted to live beside humans in a novel environment modified by men ([Bidau, 2009](#)). Thousands of years of selection for traits desired by humans have led to tremendous phenotype diversity in domesticated animals, which is not present in laboratory animals. Although various domesticated animals were under different selection pressures, all of them share the trait of tameness, i.e., they are less fearful of humans and sometimes even strive for human contact or handling ([Jensen et al., 2008](#); [Albert et al., 2009](#)). The wild ancestors of some domesticated animals

(dog, pig, chicken, fish, etc.) exist in the nature and their fearfulness and aggression levels are significantly different from their domesticated counterpart. The comparison of domesticated animals' genome with their wild ancestors provides a unique opportunity for us to study the genetic basis of fearfulness and stress response ([Andersson, 2012](#)).

In this review, I will present the current knowledge on the genetic contribution in shaping behaviours, focusing on the genes involved in regulation of fear and stress in various animals. At the end, the effects of artificial selection for traits desired by humans on domesticated animals' behaviour and welfare will be reviewed.

3 Single genes influencing behaviour

It is well accepted that genes, environment and the interactions between them regulate behaviour ([Robinson, 2004](#)). The presented genes are well-studied examples of single genes influencing different behavioural patterns. The *period* gene (*per*) regulating circadian behaviour was first described in *Drosophila* ([Konopka and Benzer, 1971](#)). Three naturally occurring mutations of the *per* gene are responsible for the phenotypic diversity of the trait. The normal daily rhythm of *Drosophila* is 24 hours and 3 mutations have been found that can alter this pattern drastically. One mutation (*per^s*) leads to 19 hours daily rhythm, another one (*per^l*) causes 28 hours daily pattern and the flies carrying the third mutation (*per⁰*) have an arrhythmic circadian pattern ([Konopka and Benzer, 1971](#)). The *period* gene is also involved in producing court ship song in *Drosophila* ([Wheeler et al., 1991](#)). When a small fragment of *D. melanogaster* was transferred to *D. simulans*, they performed the mating song of *D. melanogaster* instead of their own species specific song.

Another example of a single gene influencing a complex behaviour is the foraging gene (*for*) which regulates food searching behaviour of the *D. melanogaster*. The gene encodes a cGMP- dependent protein kinase (PKG), and there are two naturally occurring alleles for the gene, namely, rover allele (*for^R*), and sitter allele (*for^s*). The *for^R* homozygous flies travel more during food consumption in comparison to both *for^s* homozygous and *for^s/for^R* flies and the flies with the *for^R* allele have higher brain PKG activity and more *for* brain expression ([Sokolowski, 1980](#); [Osborne et al., 1997](#); [Ben-Shahar et al., 2002](#)). Shahar et al. ([Ben-Shahar et al., 2002](#)) showed that the increased *for* gene expression caused young honey bees to start foraging instead of hive work, and the expression of the gene depends both on genetic variation and the colony's need for foragers. The

for gene is an example of behavioural genes with conserved functions in different invertebrate species.

Experiments with voles have shown how variation on a single gene can alter brain expression of a receptor and cause substantial behavioural changes ([Insel and Young, 2001](#)). Vasopressin is a hormone related to pair bonding and attachment to the offspring. The *AVPR 1a* gene, which encodes for the arginine vasopressin receptor 1A, plays a significant role in the social behaviour of voles ([Insel and Young, 2001](#)). In contrast to 95 % of mammals who are polygamous, the male prairie vole (*Microtus ochrogaster*) bonds with the female after mating. Polymorphism in promoter of *AVPR 1a* gene is responsible for differences in receptor distribution and behaviour of prairie vole. Transgenic male mice with the prairie vole *AVPR 1a* allele bonded with females in response to vasopressin ([Insel and Young, 2001](#); [Robinson, 2004](#)). *AVPR 1a* also seems to play a role in human pair bonding. More than 550 Swedish twin pairs were studied to find an association between genetic variability of *AVPR 1a* and the partner bonding parameters of the subjects ([Walum et al., 2008](#)). In males, one variation on allele RS3 334 was found to be related to lower pair bonding scores. The homozygous males for the allele had significantly higher chance of having marital problems. But more functional-and gene expression studies should be conducted before coming to a conclusion about the role of a single gene in a very complex and multifactorial human traits such as pair fidelity ([Donaldson and Young, 2008](#)).

The forkhead box P2 gene (*FoxP2*), which encodes an important transcription factor, is the candidate gene involved in memory and vocal learning of song birds ([Haesler et al., 2004](#)). An orthologue of *FoxP2* is also involved in language learning in human and a mutation on the gene causes a severe speech and language disorder ([Lai et al., 2001](#)).

The molecular pathways which link single genes to behaviours are mostly obscure because of the polygenic inheritance and complexity of behavioural traits. The underlying neural pathways which link *for* gene with already mentioned behavioural polymorphisms in foraging behaviour of *D. melanogaster* have been studied extensively. Osborne et al. showed that the flies with rover allele have higher brain PKG activity and *for* expression ([Osborne et al., 1997](#)). The differences in physiological characteristics of neurons in rovers and sitters were studied by Renger et al. ([Renger et al., 1999](#)). It was shown that sitters have lower neural voltage-dependent K⁺ current and also have different neural excitability patterns ([Renger et al., 1999](#)). PKG activity also plays a role in feeding related behaviour in nematodes, e.g. in *Caenorhabditis*

elegans, and a mutation that causes decreased PKG activity would also lead to higher locomotion ([Robinson et al., 2005](#)). The PKG signaling pathway seems to be related to locomotion and food searching behaviour of flies, bees and nematodes, but the methods of the regulation is different among mentioned species.

Animals use their sensory organs to perceive the environment and hence the modification of sensory systems can lead to changes in behavioural patterns. For instance, the adaptation of *C. elegans* to laboratory condition (growth at high density) was caused by deletion of two genes encoding pheromone receptors ([McGrath et al., 2011](#)). The modification of the chemoreceptor genes (*srg -36* and *-37*) happened as a rapid adaptation to a certain environment. McBride et al. showed that the *D. secheilla*, which is a specialized vinegar fly has different repertoire of olfactory receptor as an adaptation to the new ecological niche ([McBride, 2007](#)). The genetic changes of sensory receptors can modify specific behaviour without major deleterious effects due to pleiotropy.

Another pathway that can link genes to behaviour is associated with G-protein coupled receptors and internal motivation states. *Rgs2* which is related to anxiety in mice and *AVPR 1a* which is related to pair bonding in voles are example of the genes that influence behaviour via a neuromodulatory pathway ([Bendesky and Bargmann, 2011](#)). Some of these pathways are conserved in various animals, for example Bendesky et al. showed that polymorphism in the *tyra-3* gene (tyramine receptor 3) which encodes a catecholamine receptor, affect decision making to leave the colony and foraging behaviour in nematode *C. elegans*. The authors suggested catecholamines have conserved function in modulating behavioural decisions ([Bendesky et al., 2011](#)).

4 The influence of the environment on gene expression and behaviour

Although genetic variation plays a fundamental role in shaping behaviour, environment and epigenetics can extensively influence behaviours. Non-sequence based modifications of the DNA which alters the expression pattern of genes and can be heritable are termed epigenetics ([Goldberg et al., 2007](#)), in other words, when the final outcome of a locus changes in the absence of change in the related DNA sequence. Three main mechanisms have been associated with epigenetics, namely, cytosine methylation, histone modification and non-coding RNAs ([Bernstein et al., 2007](#)). A family of proteins called DNA

methyltransferases, mediate cytosine methylation by adding methyl groups to cytosine in CpG pairs ([Goll and Bestor, 2005](#)). The biological significance of cytosine methylation has been a matter of controversy for a long time. The recent studies suggest that the methylation of genome regions which contain high density of CpGs (CpG islands) is correlated with suppressed expression of the gene ([Goll and Bestor, 2005](#)). Histones are the proteins which act as the core for the DNA to circle around and form chromatin and they are also involved in gene regulation. The histones can be subjected to various modifications such as acetylation, methylation, phosphorylation, etc. The functions of most of these modifications are not yet clear but recent progress in molecular biology is helping us to understand the function of histone modification in gene regulation and epigenetics ([Bernstein et al., 2007](#)). Another recently suggested mechanism controlling epigenetics is mediated by RNA and especially by noncoding RNAs ([Bernstein and Allis, 2005](#)). The mentioned mechanisms, their interaction together and probably, yet to be discovered pathways play a role in modulating epigenetic phenomena ([Goldberg et al., 2007](#)).

Weaver et al. ([Weaver et al., 2002](#)) showed that maternal care influences the stress response in rat pups by altering the expression of glucocorticoid receptors (GR) in the hippocampus. As adults, the offspring of mothers performing high frequency of pup licking/grooming are behaviourally less fearful and show milder hypothalamic-pituitary-adrenal (HPA) response to stress in comparison to those that received less nursing ([Weaver et al., 2002](#)). The variation in maternal behaviour of rats is inherited, i.e. offspring that receive less attention from their mother do the same to their offspring when they grow up ([Francis et al., 1999](#)). The mentioned inherited behavioural variations and gene expression happen in the absence of genetic diversity and via epigenetics and DNA methylation ([Weaver et al., 2002](#)). It was shown that high levels of maternal care would cause histone acetylation and DNA demethylation at hippocampus GR gene promoter, leading to changes in GR expression and different HPA response to stress ([Weaver et al., 2004](#)). Cross fostering experiments led to reversed epigenetic changes after one week and the differences among the two groups continued into adulthood.

Caspi et al. studied the genotype \times environment interaction in modulation of stress and depression in humans ([Munari et al., 2012](#)). It was shown that a functional polymorphism in the promoter of 5-*HTT* gene which encodes a serotonin transporter influences the response of individuals to stressful life events. Individuals who had a specific polymorphism on 5-*HTT* promoter (short allele) were influenced more dramatically (higher

suicide tendency and diagnosable depression) by stressful life events. Individuals who had the “short” allele on the *5-HTT* gene showed higher amygdala neuronal activity after being exposed to fearful stimuli in functional magnetic resonance imaging (fMRI), which may be the reason for the association between the mentioned allele and being more fearful in humans([Hariri et al., 2002](#)).

Nätt et al. hypothesized that chickens raised under chronic stress, such as unpredictable food access, would adapt to the situation by modifying their feeding and social behaviour and predicted that these behavioural adaptations would be inherited to the offspring ([Nätt et al., 2009](#)). Parents were reared in two groups; in one group they received regular daily light rhythm (RL), while the other group was raised under irregular daily light rhythm (IL). In comparison to RL birds, the birds raised under IL chose freely available food rather than the more attractive but hidden food. Interestingly, as adults the female offspring of IL birds also adapted similar foraging behaviour as their mothers, they showed higher tendency to feed on high energy food, were heavier, showed more dominant behaviour and had a higher survival rate. The reported high levels of egg yolk estradiol in IL birds can be a potential mechanism for the inherited behavioural differences.

5 Domestication experiments

In 1959, Dmitry K. Belyaev, a Russian geneticist started to select and breed foxes solely based on their tameness ([Belyaev, 1979](#)). After only a few generations, the behaviour of selected groups began to change from the non-selected foxes. The animals from the selected population were not afraid of humans and even started to seek human contact. Interestingly, beside the radical behavioural modifications, the tame foxes had altered reproductive function, their coat colour changed and some of them developed drooping ears which is a characteristic of young dogs and some other domesticated animals ([Belyaev, 1979](#)). Considering the findings of the experiment, Belyaev figured that the traditional genetic framework can't explain the extensive variety of observed changes in the group that were selected based exclusively on tameness and he introduced the idea of destabilization selection as a factor of domestication ([Belyaev, 1979](#); [Trut, 1999](#)). When an organism is well adapted to a certain environment, the stabilizing selection suppresses or eliminates the effects of mutations that alter the normal phenotype in order to keep the optimal phenotypic development to the environment. When the selection pressure changes, destabilizing selection acts to

reverse stabilizing selection by disrupting the morphology and the physiology of the organism that had been stabilized to the previous natural selection ([Trut et al., 2009](#)). The genetic changes behind these morphological and behavioural changes are not clear and epigenetic modification has been suggested to play a major role. Considering that only a few HPA axis related genes have been shown to be differently expressed in tame foxes, it can be hypothesized that the change in the expression of a few brain genes with numerous regulatory effects have led to phenotypic destabilization ([Trut et al., 2009](#)).

In the 70s, Belyaev also started a project to domesticate wild grey rats with the similar method that he already applied in the fox domestication project. The rats have been selected according to their aggression level toward humans for more than 60 generation. Similar to the fox experiment the tame rats are not aggressive toward humans anymore, tolerate handling and sometimes even approach humans in a non-aggressive manner, while the aggressive lines attack or run away from humans. Similar to the tame foxes, the white spots also appeared in tame rats, bringing up the idea that maybe the same loci that control tameness are also involved in coat colour ([Albert et al., 2009](#); [Plyusnina et al., 2011](#)). The white colour coat is more common in domesticated animals in comparison to wild ones and various explanations have been suggested. Rosengren Pielberg et al. suggested that direct selection for specific colour variants by humans and the removal of need for camouflage during domestication are possible explanations for the high prevalence of white colour coat phenotype in domesticated animals ([Rosengren Pielberg et al., 2008](#)). Another probable explanation is that there is pleiotropy between certain colour variants and behaviour such as tameness. In both rats and deer mice, it was shown that certain coat variants (nonagouti) are easier to handle, less aggressive and less active ([Hayssen, 1997](#)).

6 Stress and aggression: Typical examples of quantitative traits

Traits which are affected by multiple genetic factors are known as quantitative traits. A region in chromosome that has one or more genes that affect a quantitative trait is termed as quantitative trait loci (QTL) ([Andersson, 2001](#)). Most behaviour are typical quantitative traits, and are shaped through a network of several interacting genes. They are also extremely sensitive to the environment and even genetically identical individuals can have different behavioural phenotypes ([Anholt and Mackay, 2004](#)). Recent studies suggest that the distribution of allelic

effects is exponential in quantitative traits. A few loci which have big effects (major genes) cause most of the difference between strains, and a progressively larger number of loci with progressively smaller effects (minor genes) contribute to the rest of the difference ([Mackay, 2001](#)). Flint (2003) reviewed QTL that influence different behaviour and reported 94 QTL that affect behaviour in different animals ([Flint, 2003](#)), but the responsible genes behind most QTL are still not clear.

The genetic components underlying biomedically important traits such as anxiety, depression and aggression have been studied extensively in recent years, mostly using rodents as a model ([Yalcin et al., 2004](#)). A large number of QTL have been reported to affect different stress related behaviours but the underlying responsible genes are mostly obscure ([Flint, 2003](#)). One problematic matter in detecting the genes involved in a certain QTL is that usually each behavioural QTL has a small contribution to the phenotype. Another complication in genetic mapping of behavioural traits is that QTL analyses detects a functional variant and not a gene, while the functionally important variant that affects gene expression might lie far from their related genes, e.g. in an intron of an unrelated gene ([Lettice et al., 2002](#); [Nobrega et al., 2003](#)). In spite of difficulties in finding the genes underlying behavioural QTL, a few candidate genes have been found to modulate the effect of some QTL.

In a study aiming to find the QTL for anxiety related behaviour in mice, 1671 mice were subjected to a variety of behavioural tests, such as an open field test, a dark-light emergency test, a mirror-chamber test, and a square maze, leading to recognition of more than 100 anxiety related variables in rodents ([Henderson et al., 2004](#)). Significant and consistent QTL were found on chromosomes 1, 4, 7, 8, 14, 15, 18, and X. The locomotor activity was related to two QTL, on chromosomes 4 and 8, while anxiety-related behaviours were influenced by QTL on chromosomes 1, 15 and 18 ([Henderson et al., 2004](#)). Applying a high resolution mapping method, Yalcin et.al ([Yalcin et al., 2004](#)) studied the anxiety related QTL region on chromosome 1, and showed that the *Rgs2* gene which encodes a regulator of G protein signaling, is the gene candidate responsible for the QTL and is involved in mouse anxiety. Later studies with *Rgs2* knockout mice out revealed that the mice lacking *Rgs2* showed more anxiety related behaviour ([Yalcin et al., 2004](#)).

To map the loci for aggressiveness and tameness in foxes, several intercross and backcross populations between tame and aggressive lines were generated ([Kukekova et al., 2011](#); [Kukekova et al., 2012](#)). Tame behaviour was associated with loci on fox chromosome 12 (VVU12). The DNA region is the ortholog of a region in dogs and wolves and has been

associated with canine domestication ([vonHoldt et al., 2010](#); [Kukekova et al., 2011](#)). But VVU12 mapping profiles were significantly different between different crosses and even between similar crosses that had different parents. The findings suggest that the expression of these loci depends on the genome context and highlight the role of epistasis (when genes modify effects of each other).

To study the genetic basis of aggression and tameness, more than 700 rats from an intercross between tame and aggressive lines were subjected to various behavioral, physiological and morphological tests (tameness, aggression, anxiety, organ weight, coat colour, and catecholamine and corticosterone level in the serum). The genetic mapping revealed two significant QTL for tameness related traits, namely, Tame1 and Tame2 which overlapped with QTL for the anxiety related traits and the adrenal size. One QTL on chromosome 14 containing the *Kit* gene was found for white colour spot. The *Kit* gene is involved in melanoblast migration and probably responsible for the white colour phenotype in rats. But the coat white spotting QTL was not linked with none of the QTL for tameness, i.e. white spotting loci doesn't contribute in the tameness in the studied rat populations. The identified tameness QTL in the rat experiment did not map to orthologous regions in fox tameness loci, suggesting that multiple genetic paths can lead to evolving tameness ([Kukekova et al., 2011](#); [Plyusnina et al., 2011](#)).

To study the relation between fear response and production traits, Schütz et al ([Schütz et al., 2004](#)) studied one population of red junglefowl (RJF), one population of White Leghorn (WL), and the F2 intercross generation of WL × RJF. QTL analyses were conducted for various fear related behavioural tests (open field test [OF], novel object test [NO], tonic immobility [TI], and restraint test) and various production traits (growth, food intake, sexual maturity, and egg production). In the OF and NO tests WLs were less fearful, while the RJFs were less fearful in the TI test and were more active in the restraint test. One QTL was found on chromosome 1 for TI which also coincided with growth, a major growth QTL, and in males another significant QTL for NO was related with another main growth QTL. Several other significant behavioural QTL were also found but were not correlated with production traits ([Schütz et al., 2004](#)).

Functional studies have found a role for various genes involved in fear and anxiety ([Hovatta and Barlow, 2008](#)). For example, serotonin_{1A} receptor (*5-Ht1ar*) has been shown to play a role in anxiety related behavioural traits, and mice lacking the receptor (*5-Ht1ar* knock-out) demonstrate enhanced anxiety-like behaviour in tests such as avoiding the

fearful and novel environment and running away from stressful situations ([Parks et al., 1998](#); [Gross et al., 2002](#)).

7 The genetic architecture of behaviour in domesticated animals

The behaviour of the domestic dog has been shaped during 14000 years of artificial selection by humans ([Udell et al., 2010](#)). The genetic basis of their behavioural diversity is largely unknown. Akey et al. ([Akey et al., 2010](#)) have conducted a genome-wide scan searching for signatures of recent selection in different breeds of dog and found 155 genomic regions with strong signatures of recent selection. The notion behind selection mapping is that genes which regulate a significantly desired trait lie in selective sweeps (selective sweeps are parts of the genome with reduced nucleotide variation, and suggest recent positive selection). The identified sweeps contained genes involved in morphology, physiology and behaviour. *CDH9*, *DRD5*, *HTR2A* and *SEMAD3* were among candidate genes that potentially can affect behaviour ([Akey et al., 2010](#)). *CDH9* encodes a protein called cadherin 9 which is a neuronal cell-adhesion molecule. The SNP variations of *CDH9* in humans are associated with autism; a disorder of neural development characterized by abnormal social interaction and communication ([Wang et al., 2009](#)). *DRD5* encodes the dopamine D5 receptor and is mostly expressed in the limbic system of the brain, which is involved in emotion regulation, cognition and motivation ([Vanyukov et al., 2000](#)). *HTR2A* encodes serotonin 5-HT_{2A} receptor and plays various roles in learning, anxiety and behaviour ([Hoyer et al., 2002](#)) and aggression in mice ([Saudou et al., 1994](#)), but not in golden retriever dog ([van den Berg et al., 2008](#)). *SEMAD3* (Semaphorin 3D) belongs to semaphorin family and is involved in neural crest cell development and cell proliferation ([Kruger et al., 2005](#)). In an extensive genome-wide survey of dogs and wolves conducted by vonHoldt ([vonHoldt et al., 2010](#)), two out of three most strong selection signatures in dog genome were found near genes involved in behaviour and memory of mice and humans, namely, ryanodine receptor 3 (*RyR3*) and adenylate cyclase 8 (*ADCY8*) ([Balschun et al., 1999](#); [vonHoldt et al., 2010](#)). Another strong sweep was found near *WBSCR17* gene, which is one of the genes being deleted in Williams–Beuren syndrome in human ([vonHoldt et al., 2010](#)). The syndrome is characterized by facial dysmorphism, mild to moderate intellectual deficits, and personality trait described as hypersociable ([Martens et al., 2008](#)). It is worth noting that ultimately experimental studies are needed to determine whether the polymorphisms of the mentioned genes are important in shaping the

behaviour of the domesticated dog. Considering great breed variability among dogs and the fact that dogs and humans share some common diseases, they are a valuable model animal to study comparative disease genetics ([Karlsson and Lindblad-Toh, 2008](#)).

The DNA sequence is almost identical in dog and wolf, Saetre et al. hypothesized that the notable difference in behaviour of the two species is the result of change in the pattern of gene expression ([Saetre et al., 2004](#)). To test the hypothesis, the gene expression patterns in hypothalamus, amygdala and frontal cortex in dogs, wolves and coyote (*Canis latrans*) were compared. The most noticeable change in the gene expression between dog and wolf was found in hypothalamus, which is involved in variety of behavioural and physiological responses. The authors suggested that during domestication, the intensive evolutionary pressure for behaviour has led to change in the expression pattern of a few multifunctional hypothalamic genes with big downstream effects on various traits ([Saetre et al., 2004](#)).

The red jungle fowl (*Gallus gallus*) is the main ancestor of all breeds of chicken ([Eriksson et al., 2008](#)). The chickens' great breed variability plus the fact that they can be hatched and reared in controlled environments have made them a proper model to study the genetic basis of rapid adaptation ([Jensen and Andersson, 2005](#)). To get insight into the genetic basis of chicken domestication, Rubin et al. sequenced the genome of various domesticated breeds and the ancestral red junglefowl ([Rubin et al., 2010](#)). Several selective sweeps containing genes such as *PMCH*, *IGF1* and *INSR* were found in broilers. These genes are involved in appetite regulation, growth and metabolism. A few genes that may be involved in behaviour were also highlighted, namely, *SEMA3A* which plays an important role in brain development (54), *ADRA2C*, which codes for the alpha 2c adrenergic receptor with broad physiological and behavioural roles ([Philipp and Hein, 2004](#)) and *TSHR* gene.

The *TSHR* gene encodes thyroid stimulating hormone receptor and lies in a selective sweep, which suggests that it might had been the subject of recent selection in the domesticated chickens ([Rubin et al., 2010](#)). To investigate whether other populations of domesticated chicken also carry the mutant allele, 271 birds from 36 populations with different geographical origin were genotyped for the *TSHR* region. Interestingly, 264 out of 271 tested birds were homozygous for the sweep haplotype and the rest were heterozygous. Considering the vast genetic diversity of chickens, this finding suggests that *TSHR* may be related to chicken domestication ([Rubin et al., 2010](#)). The locus containing *TSHR* did not coincide with any of already found 13 growth QTL, and hence probably

the sweep haplotype doesn't play a major role in metabolism and growth. On the other hand, *TSHR* is also associated with a classic characteristic of most domesticated animals, namely, the lack of a strict seasonal reproduction pattern. Recent findings have revealed the role of *TSHR* in photoperiod regulation of reproduction ([Yoshimura et al., 2003](#); [Hanon et al., 2008](#); [Nakao et al., 2008](#); [Ono et al., 2009](#)).

Most temperate zone birds have a strict seasonal reproduction pattern and have evolved photoperiodic time measurement to anticipate and adapt to the seasonal changes ([Dawson et al., 2001](#)). Unlike mammals, birds do not mainly relay on melatonin signals to measure day length ([Juss et al., 1993](#)). Instead, it has been shown that the luteinizing hormone (LH) surge that happens after long days is responsible for reproductive photoperiodism ([Nicholls et al., 1983](#)). The mediobasal hypothalamus (MBH) is involved in measuring daylight and modulates the secretion of gonadotropin-releasing hormone (GnRH) in the quail, and thyroid hormone metabolism (T_4 to T_3 conversion) is involved in activating this pathway ([Yoshimura et al., 2003](#)). Type 2 deiodinase (DIO2) converts T_4 (prohormone thyroxine) to T_3 (bioactive triiodothyronine), and Type 3 deiodinase (DIO3) has an opposite action by converting T_4 to T_3 and T_3 to T_2 . During short days, DIO2 is expressed at low level, while DIO3 is expressed in high level, but after a long day the expression pattern of DIO2 and DIO3 is reversed, resulting in local accumulation of T_3 in MBH ([Yoshimura et al., 2003](#); [Nakao et al., 2008](#)). High levels of T_3 in MBH lead to LH surge and also administration of T_3 to the birds living in short days leads to increase of the level of plasma LH ([Follett and Nicholls, 1988](#); [Yasuo et al., 2005](#)). Nakao et al. ([Nakao et al., 2008](#)) recognized two waves of gene expression in pars tuberalis (a part of the anterior pituitary lobe) in the quail brain. The TSH expression increased 14 hours after the end of the first long day followed by an increase in DIO2 expression in 4 hours. When the birds living in short day environments received TSH via intracerebroventricular (ICV) injection, their gonads started to grow and the expression level of DIO2 increased in their pars tuberalis ([Nakao et al., 2008](#)). Hence, the authors suggested that the expression of TSH in pars tuberalis might initiate the activation of photoinduced seasonal breeding. The exact role of *TSHR* on regulating circadian photoperiodism is not clear, but humans who have a mutation on the *TSHR* gene have elevated plasma TSH. The role of *TSHR* in chicken domestication is a matter of on-going studies at Linköping University.

Another gene which affects both morphology and behaviour is the *PMEL17* gene. Using an intercross between the red jungle fowl and

White Leghorn chickens, Keeling et al. ([Keeling et al., 2004](#)) studied the role of the *PMEL17* gene, which regulates plumage melanization and showed that the birds which carry the recessive wild allele (*i/i*) are more vulnerable to become targets of feather pecking in comparison the birds that are homozygous for the white allele (*I/I*). In behavioural comparison between the two genotypes, *i/i* birds vocalized more in a novel arena and were more active in the fear of human test ([Nätt et al., 2007](#)). But the authors did not exclude the negative social influence caused by being feather pecked any further. To separate direct and indirect influence of genotype, Karlsson et al. ([Karlsson et al., 2011](#)) reared the birds without social contact. The *I/I* birds were more explorative and active and showed more social interactions with the conspecifics in a test called complex environment test, but no hormonal differences were found between genotypes. The authors suggested the *PMEL17* has pleiotropic effect on behaviour ([Karlsson et al., 2011](#)).

8 The implication of genetics in improving animal welfare

The strong selection in livestock animals has led to dramatic increases in production level but it also has increased the risk of various behavioural and physiological welfare issues ([Rauw et al., 1998](#)). For instance, male turkeys can't mate naturally as they are too heavy. Chickens are also suffering from various disorders caused by selection for high production traits. It has been shown that broilers are severely suffering from constant hunger, ascites, leg problems and hampered immune response to various diseases due to their high metabolic rate and heavy weight [reviewed by Rauw et al. ([Rauw et al., 1998](#))].

Double muscling (DM) is a phenotype in bovine characterized by significant muscle hypertrophy and development in all body parts. Cattle with this phenotype have a higher number of muscle fibers (hyperplasia) and also the fibers are bigger (hypertrophy). The DM cattle have higher muscle to bone ratio and lower adipose tissue thus; they produce a larger amount of expensive meat, and hence, the DM phenotype has been favored by farmers ([Arthur et al., 1989](#)). The suppression of *Myostatin* gene (GDF8) which is a differentiation and growth factor is the causative factor of the phenotype. Six mutations have been identified to be involved in deactivation of *Myostatin* leading to the double muscling ([Bellinge et al., 2005](#)). But unfortunately DM animals suffer from various physiological problems. It has been shown that DM cows have significantly smaller pelvic opening and, hence, suffer from dystocia (abnormal or difficult childbirth or labour) three times more often than

normal cows ([Arthur et al., 1988](#)). They also have decreased stress tolerance and higher calf mortality ([Arthur et al., 1989](#)).

Another example of negative consequence of artificial selection on animal welfare is the white coat phenotype of horses. The grey horses (white horses are scientifically termed grey) born with different colours but they start to turn grey at very young age and usually turn completely grey by the age of 6-8 years ([Andersson, 2012](#)). The grey horses have been considered charismatic throughout the history and probably have been selected uniquely based on their appearance. Rosengren Pielberg et al. suggested that a mutation on cis-regulatory region of *STX17* (syntaxin17) would cause overexpression of *STX17* and the neighboring *NR4A3* gene and lead to early and gradual loss of hair pigmentation ([Rosengren Pielberg et al., 2008](#)). But the white coat colour has been linked with very high incidence of melanomas and the grey skin phenotype is a risk factor. It is worth noting that most of these tumors are benign, but some of them can turn into widespread and deadly melanoma ([Fleury et al., 2000](#)).

Feather pecking, social stress and fear are considered as the main behavioural problems that threat the welfare of poultry industry ([Jones and Hocking, 1999](#)). It has been shown that stress response and feather pecking are heritable and the underlying QTL have been found in laying hens ([Buitenhuis et al., 2003](#)). Finding the genetic determinants of undesirable behaviours can provide applied tools to breed the future animals simultaneously on their high production level and their welfare issues such as lower stress response and reduction of abnormal behaviour such as feather pecking ([Jensen et al., 2008](#)).

9 Conclusion

The genetic architecture of behaviour is complicated and the behavioural variation is determined by the genes and the environment and their interaction. The recent advances in molecular genetics have provided a valuable tool to study the genetic basis of complex behaviour such as anxiety and aggression. By comparing the genome of domesticated animals and their wild counterparts we got insights in genes that underlie morphology and behaviour.

10 References

- Akey, J.M., Ruhe, A.L., Akey, D.T., Wong, A.K., Connelly, C.F., Madeoy, J., Nicholas, T.J., Neff, M.W., 2010. Tracking footprints of artificial selection in the dog genome. *Proceedings of the National Academy of Sciences of the United States of America* 107, 1160-1165.
- Albert, F.W., Carlborg, O., Plyusnina, I., Besnier, F., Hedwig, D., Lautenschlager, S., Lorenz, D., McIntosh, J., Neumann, C., Richter, H., Zeising, C., Kozhemyakina, R., Shchepina, O., Kratzsch, J., Trut, L., Teupser, D., Thiery, J., Schoneberg, T., Andersson, L., Paabo, S., 2009. Genetic architecture of tameness in a rat model of animal domestication. *Genetics* 182, 541-554.
- Andersson, L., 2001. Genetic dissection of phenotypic diversity in farm animals. *Nature reviews. Genetics* 2, 130-138.
- Andersson, L., 2012. How selective sweeps in domestic animals provide new insight into biological mechanisms. *J. Intern. Med.* 271, 1-14.
- Anholt, R.R.H., Mackay, T.F.C., 2004. Quantitative genetic analyses of complex behaviours in *Drosophila*. *Nature reviews. Genetics* 5, 838-849.
- Arthur, P., Makarechian, M., Price, M., Berg, R., 1989. Heterosis, maternal and direct effects in double-muscled and normal cattle: II. Carcass traits of young bulls. *J Anim Sci* 67, 911.
- Arthur, P.F., Makarechian, M., Price, M.A., 1988. Incidence of dystocia and perinatal calf mortality resulting from reciprocal crossing of double-muscled and normal cattle. *The Canadian Veterinary Journal* 29, 163.
- Balschun, D., Wolfer, D.P., Bertocchini, F., Barone, V., Conti, A., Zuschratter, W., Missiaen, L., Lipp, H.-P., Frey, J.U., Sorrentino, V., 1999. Deletion of the ryanodine receptor type 3 (RyR3) impairs forms of synaptic plasticity and spatial learning. *EMBO J* 18, 5264-5273.
- Bellinge, R., Liberles, D., Iaschi, S., 2005. Myostatin and its implications on animal breeding: a review. *Anim Genet* 36, 1-6.
- BELYAEV, D.K., 1979. Destabilizing selection as a factor in domestication. *Journal of Heredity* 70, 301-308.

- Ben-Shahar, Y., Robichon, A., Sokolowski, M.B., Robinson, G.E., 2002. Influence of Gene Action Across Different Time Scales on Behavior. *Science* 296, 741-744.
- Bendesky, A., Bargmann, C.I., 2011. Genetic contributions to behavioural diversity at the gene-environment interface. *Nature reviews. Genetics* 12, 809-820.
- Bendesky, A., Tsunozaki, M., Rockman, M.V., Kruglyak, L., Bargmann, C.I., 2011. Catecholamine receptor polymorphisms affect decision-making in *C. elegans*. *Nature* 472, 313-318.
- Bernstein, B.E., Meissner, A., Lander, E.S., 2007. The Mammalian Epigenome. *Cell* 128, 669-681.
- Bernstein, E., Allis, C.D., 2005. RNA meets chromatin. *Genes Dev* 19, 1635.
- Bidau, C.J., 2009. Domestication through the Centuries: Darwin's Ideas and Dmitry Belyaev's Long-Term Experiment in Silver Foxes. *Gayana (Concepción)* 73, 55-72.
- Buitenhuis, A., Rodenburg, T., van Hierden, Y., Siwek, M., Cornelissen, S., Nieuwland, M., Crooijmans, R., Groenen, M., Koene, P., Korte, S., Bovenhuis, H., van der Poel, J., 2003. Mapping quantitative trait loci affecting feather pecking behavior and stress response in laying hens. *Poult Sci* 82, 1215-1222.
- Dawson, A., King, V.M., Bentley, G.E., Ball, G.F., 2001. Photoperiodic Control of Seasonality in Birds. *J Biol Rhythms* 16, 365-380.
- Donaldson, Z.R., Young, L.J., 2008. Oxytocin, Vasopressin, and the Neurogenetics of Sociality. *Science* 322, 900-904.
- Eriksson, J., Larson, G., Gunnarsson, U., Bed'hom, B., Tixier-Boichard, M., Strömstedt, L., Wright, D., Jungerius, A., Vereijken, A., Randi, E., Jensen, P., Andersson, L., 2008. Identification of the Yellow Skin Gene Reveals a Hybrid Origin of the Domestic Chicken. *PLoS Genet* 4, e1000010.
- Fleury, C., Berard, F., Leblond, A., Faure, C., Ganem, N., Thomas, L., 2000. The Study of Cutaneous Melanomas in Camargue-Type Gray-Skinned Horses (2): Epidemiological Survey. *Pigm Cell Res* 13, 47-51.

- Flint, J., 2003. Analysis of quantitative trait loci that influence animal behavior. *J Neurobiol* 54, 46-77.
- Follett, B.K., Nicholls, T.J., 1988. Acute effect of thyroid hormones in mimicking photoperiodically induced release of gonadotropins in Japanese quail. *Journal of Comparative Physiology B: Biochemical, Systemic, and Environmental Physiology* 157, 837-843.
- Francis, D., Diorio, J., Liu, D., Meaney, M.J., 1999. Nongenomic Transmission Across Generations of Maternal Behavior and Stress Responses in the Rat. *Science* 286, 1155-1158.
- Goldberg, A.D., Allis, C.D., Bernstein, E., 2007. Epigenetics: A Landscape Takes Shape. *Cell* 128, 635-638.
- Goll, M.G., Bestor, T.H., 2005. Eukaryotic cytosine methyltransferases. *Annu Rev Biochem* 74, 481-514.
- Gross, C., Zhuang, X., Stark, K., Ramboz, S., Oosting, R., Kirby, L., Santarelli, L., Beck, S., Hen, R., 2002. Serotonin1A receptor acts during development to establish normal anxiety-like behaviour in the adult. *Nature* 416, 396-400.
- Haesler, S., Wada, K., Nshdejan, A., Morrissey, E.E., Lints, T., Jarvis, E.D., Scharff, C., 2004. FoxP2 Expression in Avian Vocal Learners and Non-Learners. *The Journal of Neuroscience* 24, 3164-3175.
- Hanon, E.A., Lincoln, G.A., Fustin, J.-M., Dardente, H., Masson-Pévet, M., Morgan, P.J., Hazlerigg, D.G., 2008. Ancestral TSH Mechanism Signals Summer in a Photoperiodic Mammal. *Curr Biol* 18, 1147-1152.
- Hariri, A.R., Mattay, V.S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., Egan, M.F., Weinberger, D.R., 2002. Serotonin Transporter Genetic Variation and the Response of the Human Amygdala. *Science* 297, 400-403.
- Hayssen, V., 1997. Effects of the nonagouti coat-color allele on behavior of deer mice (*Peromyscus maniculatus*): A comparison with Norway Rats (*Rattus norvegicus*). *J Comp Psychol* 111, 419-423.
- Henderson, N.D., Turri, M.G., DeFries, J.C., Flint, J., 2004. QTL Analysis of Multiple Behavioral Measures of Anxiety in Mice. *Behav Genet* 34, 267-293.

- Hovatta, I., Barlow, C., 2008. Molecular genetics of anxiety in mice and men. *Ann Med* 40, 92-109.
- Hoyer, D., Hannon, J.P., Martin, G.R., 2002. Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol. Biochem. Behav.* 71, 533-554.
- Insel, T.R., Young, L.J., 2001. The neurobiology of attachment. *Nat Rev Neurosci* 2, 129-136.
- Jensen, P., 2006. Domestication—From behaviour to genes and back again. *Applied Animal Behaviour Science* 97, 3-15.
- Jensen, P., Andersson, L., 2005. Genomics Meets Ethology: A New Route to Understanding Domestication, Behavior, and Sustainability in Animal Breeding. *Ambio* 34, 320-324.
- Jensen, P., Buitenhuis, B., Kjaer, J., Zanella, A., Mormède, P., Pizzari, T., 2008. Genetics and genomics of animal behaviour and welfare—Challenges and possibilities. *Applied Animal Behaviour Science* 113, 383-403.
- Jones, R., Hocking, P., 1999. Genetic selection for poultry behaviour: big bad wolf or friend in need? *Animal Welfare* 8, 343-359.
- Juss, T.S., Meddle, S.L., Servant, R.S., King, V.M., 1993. Melatonin and Photoperiodic Time Measurement in Japanese Quail (*Coturnix coturnix japonica*). *Proc. R. Soc. Lond. B. Biol. Sci.* 254, 21-28.
- Karlsson, A.-C., Mormede, P., Kerje, S., Jensen, P., 2011. Genotype on the Pigmentation Regulating <i>PMEL17</i> Gene Affects Behavior in Chickens Raised Without Physical Contact with Conspecifics. *Behav Genet* 41, 312-322.
- Karlsson, E.K., Lindblad-Toh, K., 2008. Leader of the pack: gene mapping in dogs and other model organisms. *Nature reviews. Genetics* 9, 713-725.
- Keeling, L., Andersson, L., Schutz, K.E., Kerje, S., Fredriksson, R., Carlborg, O., Cornwallis, C.K., Pizzari, T., Jensen, P., 2004. Chicken genomics: Feather-pecking and victim pigmentation. *Nature* 431, 645-646.

- Konopka, R.J., Benzer, S., 1971. Clock Mutants of *Drosophila melanogaster*. *Proceedings of the National Academy of Sciences* 68, 2112-2116.
- Koolhaas, J.M., Bartolomucci, A., Buwalda, B., de Boer, S.F., Flügge, G., Korte, S.M., Meerlo, P., Murison, R., Olivier, B., Palanza, P., Richter-Levin, G., Sgoifo, A., Steimer, T., Stiedl, O., van Dijk, G., Wöhr, M., Fuchs, E., 2011. Stress revisited: A critical evaluation of the stress concept. *Neuroscience & Biobehavioral Reviews* 35, 1291-1301.
- Korte, S.M., Koolhaas, J.M., Wingfield, J.C., McEwen, B.S., 2005. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. *Neuroscience & Biobehavioral Reviews* 29, 3-38.
- Kruger, R.P., Aurandt, J., Guan, K.-L., 2005. Semaphorins command cells to move. *Nat Rev Mol Cell Biol* 6, 789-800.
- Kukekova, A.V., Temnykh, S.V., Johnson, J.L., Trut, L.N., Acland, G.M., 2012. Genetics of behavior in the silver fox. *Mammalian genome : official journal of the International Mammalian Genome Society* 23, 164-177.
- Kukekova, A.V., Trut, L.N., Chase, K., Kharlamova, A.V., Johnson, J.L., Temnykh, S.V., Oskina, I.N., Gulevich, R.G., Vladimirova, A.V., Klebanov, S., Shepeleva, D.V., Shikhevich, S.G., Acland, G.M., Lark, K.G., 2011. Mapping Loci for fox domestication: deconstruction/reconstruction of a behavioral phenotype. *Behavior genetics* 41, 593-606.
- Lai, C.S.L., Fisher, S.E., Hurst, J.A., Vargha-Khadem, F., Monaco, A.P., 2001. A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature* 413, 519-523.
- Lettice, L.A., Horikoshi, T., Heaney, S.J.H., van Baren, M.J., van der Linde, H.C., Breedveld, G.J., Joosse, M., Akarsu, N., Oostra, B.A., Endo, N., Shibata, M., Suzuki, M., Takahashi, E., Shinka, T., Nakahori, Y., Ayusawa, D., Nakabayashi, K., Scherer, S.W., Heutink, P., Hill, R.E., Noji, S., 2002. Disruption of a long-range cis-acting regulator for *Shh* causes preaxial polydactyly. *Proceedings of the National Academy of Sciences* 99, 7548-7553.
- Mackay, T.F.C., 2001. Quantitative trait loci in *Drosophila*. *Nature reviews. Genetics* 2, 11-20.

Martens, M.A., Wilson, S.J., Reutens, D.C., 2008. Research Review: Williams syndrome: a critical review of the cognitive, behavioral, and neuroanatomical phenotype. *Journal of Child Psychology and Psychiatry* 49, 576-608.

McBride, C.S., 2007. Rapid evolution of smell and taste receptor genes during host specialization in *Drosophila sechellia*. *Proceedings of the National Academy of Sciences* 104, 4996.

McEwen, B.S., 2000. Stress, definition and concepts of. Fink, G ed. Academic Press, San Diego.

McEwen, B.S., Stellar E., 1993. Stress and the individual: Mechanisms leading to disease. *Arch. Intern. Med.* 153, 2093-2101.

McEwen, B.S., Wingfield, J.C., 2003. The concept of allostasis in biology and biomedicine. *Hormones and Behavior* 43, 2-15.

McGrath, P.T., Xu, Y., Ailion, M., Garrison, J.L., Butcher, R.A., Bargmann, C.I., 2011. Parallel evolution of domesticated *Caenorhabditis* species targets pheromone receptor genes. *Nature* 477, 321-325.

Munari, F., Soeroes, S., Zenn, H.M., Schomburg, A., Kost, N., Schroeder, S., Klingberg, R., Rezaei-Ghaleh, N., Stuetzer, A., Gelato, K.A., Walla, P.J., Becker, S., Schwarzer, D., Zimmermann, B., Fischle, W., Zweckstetter, M., 2012. Methylation of K9 in histone H3 directs alternative modes of highly dynamic interaction of heterochromatin protein hHP1beta with the nucleosome. *The Journal of biological chemistry*.

Nakao, N., Ono, H., Yamamura, T., Anraku, T., Takagi, T., Higashi, K., Yasuo, S., Katou, Y., Kageyama, S., Uno, Y., Kasukawa, T., Iigo, M., Sharp, P.J., Iwasawa, A., Suzuki, Y., Sugano, S., Niimi, T., Mizutani, M., Namikawa, T., Ebihara, S., Ueda, H.R., Yoshimura, T., 2008. Thyrotrophin in the pars tuberalis triggers photoperiodic response. *Nature* 452, 317-322.

Nätt, D., Kerje, S., Andersson, L., Jensen, P., 2007. Plumage Color and Feather Pecking—Behavioral Differences Associated with PMEL17 Genotypes in Chicken (<i>Gallus gallus). *Behav Genet* 37, 399-407.

Nätt, D., Lindqvist, N., Stranneheim, H., Lundeberg, J., Torjesen, P.A., Jensen, P., 2009. Inheritance of Acquired Behaviour Adaptations and Brain Gene Expression in Chickens. *PLoS ONE* 4, e6405.

Nicholls, T.J., Follett, B.K., Robinson, J.E., 1983. A photoperiodic response in gonadectomized Japanese quail exposed to a single long day. *J Endocrinol* 97, 121-126.

Nobrega, M.A., Ovcharenko, I., Afzal, V., Rubin, E.M., 2003. Scanning Human Gene Deserts for Long-Range Enhancers. *Science* 302, 413.

Ono, H., Nakao, N., Yoshimura, T., 2009. Identification of the photoperiodic signaling pathway regulating seasonal reproduction using the functional genomics approach. *Gen Comp Endocrinol* 163, 2-6.

Osborne, K.A., Robichon, A., Burgess, E., Butland, S., Shaw, R.A., Coulthard, A., Pereira, H.S., Greenspan, R.J., Sokolowski, M.B., 1997. Natural Behavior Polymorphism Due to a cGMP-Dependent Protein Kinase of *Drosophila*. *Science* 277, 834-836.

Parks, C.L., Robinson, P.S., Sibille, E., Shenk, T., Toth, M., 1998. Increased anxiety of mice lacking the serotonin1A receptor. *Proceedings of the National Academy of Sciences* 95, 10734-10739.

Philipp, M., Hein, L., 2004. Adrenergic receptor knockout mice: distinct functions of 9 receptor subtypes. *Pharmacology & Therapeutics* 101, 65-74.

Plyusnina, I.Z., Solov'eva, M.Y., Oskina, I.N., 2011. Effect of domestication on aggression in gray Norway rats. *Behavior genetics* 41, 583-592.

Rauw, W.M., Kanis, E., Noordhuizen-Stassen, E.N., Grommers, F.J., 1998. Undesirable side effects of selection for high production efficiency in farm animals: a review. *Livestock Production Science* 56, 15-33.

Renger, J.J., Yao, W.D., Sokolowski, M.B., Wu, C.F., 1999. Neuronal polymorphism among natural alleles of a cGMP-dependent kinase gene, *foraging*, in *Drosophila*. *J Neurosci* 19.

Robinson, G.E., 2004. Beyond Nature and Nurture. *Science* 304, 397-399.

Robinson, G.E., Grozinger, C.M., Whitfield, C.W., 2005. Sociogenomics: social life in molecular terms. *Nature reviews. Genetics* 6, 257-270.

Rosengren Pielberg, G., Golovko, A., Sundstrom, E., Curik, I., Lennartsson, J., Seltenhammer, M.H., Druml, T., Binns, M., Fitzsimmons, C., Lindgren, G., Sandberg, K., Baumung, R., Vetterlein, M., Stromberg,

- S., Grabherr, M., Wade, C., Lindblad-Toh, K., Ponten, F., Heldin, C.-H., Solkner, J., Andersson, L., 2008. A cis-acting regulatory mutation causes premature hair graying and susceptibility to melanoma in the horse. *Nature genetics* 40, 1004-1009.
- Rubin, C.J., Zody, M.C., Eriksson, J., Meadows, J.R., Sherwood, E., Webster, M.T., Jiang, L., Ingman, M., Sharpe, T., Ka, S., Hallbook, F., Besnier, F., Carlborg, O., Bed'hom, B., Tixier-Boichard, M., Jensen, P., Siegel, P., Lindblad-Toh, K., Andersson, L., 2010. Whole-genome resequencing reveals loci under selection during chicken domestication. *Nature* 464, 587-591.
- Saetre, P., Lindberg, J., Leonard, J.A., Olsson, K., Pettersson, U., Ellegren, H., Bergström, T.F., Vilà, C., Jazin, E., 2004. From wild wolf to domestic dog: gene expression changes in the brain. *Mol. Brain Res.* 126, 198-206.
- Saudou, F., Amara, D.A., Dierich, A., LeMeur, M., Ramboz, S., Segu, L., Buhot, M.-C., Hen, R., 1994. Enhanced Aggressive Behavior in Mice Lacking 5-HTS Receptor. *Science* 265, 1875-1878.
- Schütz, K., Kerje, S., Jacobsson, L., Forkman, B., Carlborg, Ö., Andersson, L., Jensen, P., 2004. Major Growth QTLs in Fowl Are Related to Fearful Behavior: Possible Genetic Links Between Fear Responses and Production Traits in a Red Junglefowl × White Leghorn Intercross. *Behavior genetics* 34, 121-130.
- Sokolowski, M.B., 1980. Foraging strategies of *Drosophila melanogaster* : A chromosomal analysis. *Behav Genet* 10, 291-302.
- Trut, L., Oskina, I., Kharlamova, A., 2009. Animal evolution during domestication: the domesticated fox as a model. *BioEssays : news and reviews in molecular, cellular and developmental biology* 31, 349-360.
- Trut, L.N., 1999. Early Canid Domestication: The Farm-Fox Experiment: Foxes bred for tamability in a 40-year experiment exhibit remarkable transformations that suggest an interplay between behavioral genetics and development. *Am Sci* 87, 160-169.
- Udell, M.A.R., Dorey, N.R., Wynne, C.D.L., 2010. What did domestication do to dogs? A new account of dogs' sensitivity to human actions. *Biological Reviews* 85, 327-345.

van den Berg, L., Vos-Loohuis, M., Schilder, M., van Oost, B., Hazewinkel, H., Wade, C., Karlsson, E., Lindblad-Toh, K., Liinamo, A., Leegwater, P., 2008. Evaluation of the Serotonergic Genes *htr1A*, *htr1B*, *htr2A*, and *slc6A4* in Aggressive Behavior of Golden Retriever Dogs. *Behav Genet* 38, 55-66.

Vanyukov, M.M., Moss, H.B., Kaplan, B.B., Kirillova, G.P., Tarter, R.E., 2000. Antisociality, substance dependence, and the DRD5 gene: A preliminary study. *Am. J. Med. Genet.* 96, 654-658.

vonHoldt, B.M., Pollinger, J.P., Lohmueller, K.E., Han, E., Parker, H.G., Quignon, P., Degenhardt, J.D., Boyko, A.R., Earl, D.A., Auton, A., Reynolds, A., Bryc, K., Brisbin, A., Knowles, J.C., Mosher, D.S., Spady, T.C., Elkahoul, A., Geffen, E., Pilot, M., Jedrzejewski, W., Greco, C., Randi, E., Bannasch, D., Wilton, A., Shearman, J., Musiani, M., Cargill, M., Jones, P.G., Qian, Z., Huang, W., Ding, Z.-L., Zhang, Y.-p., Bustamante, C.D., Ostrander, E.A., Novembre, J., Wayne, R.K., 2010. Genome-wide SNP and haplotype analyses reveal a rich history underlying dog domestication. *Nature* 464, 898-902.

Walum, H., Westberg, L., Henningsson, S., Neiderhiser, J.M., Reiss, D., Igl, W., Ganiban, J.M., Spotts, E.L., Pedersen, N.L., Eriksson, E., Lichtenstein, P., 2008. Genetic variation in the vasopressin receptor 1a gene (*AVPR1A*) associates with pair-bonding behavior in humans. *Proceedings of the National Academy of Sciences* 105, 14153-14156.

Wang, K., Zhang, H., Ma, D., Bucan, M., Glessner, J.T., Abrahams, B.S., Salyakina, D., Imielinski, M., Bradfield, J.P., Sleiman, P.M.A., Kim, C.E., Hou, C., Frackelton, E., Chiavacci, R., Takahashi, N., Sakurai, T., Rappaport, E., Lajonchere, C.M., Munson, J., Estes, A., Korvatska, O., Piven, J., Sonnenblick, L.I., Alvarez Retuerto, A.I., Herman, E.I., Dong, H., Hutman, T., Sigman, M., Ozonoff, S., Klin, A., Owley, T., Sweeney, J.A., Brune, C.W., Cantor, R.M., Bernier, R., Gilbert, J.R., Cuccaro, M.L., McMahon, W.M., Miller, J., State, M.W., Wassink, T.H., Coon, H., Levy, S.E., Schultz, R.T., Nurnberger, J.I., Haines, J.L., Sutcliffe, J.S., Cook, E.H., Minshew, N.J., Buxbaum, J.D., Dawson, G., Grant, S.F.A., Geschwind, D.H., Pericak-Vance, M.A., Schellenberg, G.D., Hakonarson, H., 2009. Common genetic variants on 5p14.1 associate with autism spectrum disorders. *Nature* 459, 528-533.

Weaver, I.C.G., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S., Szyf, M., Meaney, M.J., 2004. Epigenetic programming by maternal behavior. *Nat Neurosci* 7, 847-854.

Weaver, I.C.G., Szyf, M., Meaney, M.J., 2002. FROM MATERNAL CARE TO GENE EXPRESSION: DNA METHYLATION AND THE MATERNAL PROGRAMMING OF STRESS RESPONSES. *Endocr. Res.* 28, 699-699.

Wheeler, D., Kyriacou, C., Greenacre, M., Yu, Q., Rutila, J., Rosbash, M., Hall, J., 1991. Molecular transfer of a species-specific behavior from *Drosophila simulans* to *Drosophila melanogaster*. *Science* 251, 1082-1085.

Yalcin, B., Willis-Owen, S.A., Fullerton, J., Meesaq, A., Deacon, R.M., Rawlins, J.N., Copley, R.R., Morris, A.P., Flint, J., Mott, R., 2004. Genetic dissection of a behavioral quantitative trait locus shows that *Rgs2* modulates anxiety in mice. *Nature genetics* 36, 1197-1202.

Yasuo, S., Watanabe, M., Nakao, N., Takagi, T., Follett, B.K., Ebihara, S., Yoshimura, T., 2005. The Reciprocal Switching of Two Thyroid Hormone-Activating and -Inactivating Enzyme Genes Is Involved in the Photoperiodic Gonadal Response of Japanese Quail. *Endocrinology* 146, 2551-2554.

Yoshimura, T., Yasuo, S., Watanabe, M., Iigo, M., Yamamura, T., Hirunagi, K., Ebihara, S., 2003. Light-induced hormone conversion of T4 to T3 regulates photoperiodic response of gonads in birds. *Nature* 426, 178-181.