University of Veterinary Medicine Budapest

Institute of Animal Breeding, Nutrition and Laboratory Animal Science

Department of Animal Breeding and Genetics

Review of Literature

Genetics of Aggressive Behaviour in Dogs

By

Nora Amdal Valen

Supervisor: Dr. Zöldág László Professor Emeritus

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Table of Contents

Abbreviations

AR – Androgen Receptor

C-BARQ – Canine Behavioural Assessment and Research Questionnaire

CI – Cephalic Index

DA – Dopamine

DBH – Dopamine Beta-Hydroxylase

DMA – Dog Mentality Assessment

DS – Domestication Syndrome

ESC – English Cocker Spaniel

FCI – Federation Cynologique Internationale

GWA – Genome-Wide Association

HPA – Hypothalamic-pituitary-adrenal

LGD – Large Guardian Dogs

MOA-A – Monoamide-Oxidase-A

QLT – Quantitative Trait Locus

SDA – Stranger-Directed Aggression

SNP – Single Nucleotide Polymorphism

VTA – Ventral Tegmental Area

5-TH – Serotonin

Introduction

Behavioural issues are common in the domestic dog and plays a role in many problems relating to animal welfare, public safety, and pet abandonment. Behavioural problems, including aggression, is a major reason as to why pets are relinquished to shelters and rescues (Salman, et al., 2000). If we could understand the heritability and genetics behind these behaviours better, it would allow us to match individuals and breeds to suitable owners with more ease and certainty.

The study of behaviour is a complex matter. Efforts have been made to understand the relationship between behaviour, natural predisposition, and nurtured responses ever since Darwin first came up with the concept of evolution (Darwin, 1859). Big steps have been made in recent times through the discovery and use of genetic mapping. As the technology has been made more accessible, genome mapping lets us compare potential genetic candidates behind complex traits not just within humans but also across different species. This research could prove useful not just to minimise the occurrence of dog attacks, pet abandonment and euthanasia rooted in behavioural issues; it could also contribute to research surrounding human psychiatric conditions and their inheritance.

Dogs represent a powerful opportunity to study behaviour and its inheritance, both specifically in canines but also across species. Because of highly attentive breeding practices that go back hundreds of years, the modern dog is practically unmatched in its genetic and phenotypical diversity. Moreover, each breed presents us with a group of individuals of similar phenotype and presumed capabilities, making them ideal for studying the relationship between inherited and learned behaviours (Figure 1). Canines have been argued to be a better model for human psychiatric conditions than the classical use of prey species such as rodents. Some pathological behavioural conditions found in canines may also be equivalent, possibly even homologous, to certain human psychiatric conditions (Overall, 2000).

Group 1	Sheepdogs and Cattledogs (apart from Swiss Cattledogs)	**Group 6**	Scent hounds and related breeds
Group 2	Pinscher and Schnauzer – Molossoid and Swiss Mountain and Cattledogs	**Group 7**	Pointing dogs
Group 3	Terriers	**Group 8**	Retrievers, flushing dogs, water dogs
Group 4	Dachshunds	**Group 9**	Companion and toy dogs
Group 5	Spitz and primitive breeds	**Group 10**	Sighthounds

Figure 1 Table of dog breeds. FCI nomenclature as of 2021. **(FCI, 2021)**

When comparing genomic data across different species using Genome-Wide Association studies, researchers have identified several relevant candidate genes underlying behaviour related to fear, anxiety, and obsessive traits in canines which are seemingly applicable candidates also in human research (Persson, et al., 2016).

Heritability of behaviour, domestication syndrome

There have been extensive studies made on the domestication process of animals; in essence the creation of animals kept for human purposes which were not afraid, nor aggressive towards people, compared to their wild counterparts. Scientists as far back as Darwin have noted morphological patterns across all domestic species (Figure 2). Darwin noted in the first chapter *On the Origin of Species* that "not a single domestic animal can be found which has not in some country drooping ears" (Darwin, 1859).

Darwin was unable to explain his findings through genetics; a field not yet in existence when he published his observations in The Origin of Species (1859), and later The Variation of Plants and Animals under Domestication (1868). Instead, he simply observed and categorized domestic animals and their features. Interestingly, his observations revealed a pattern of behaviours and morphologies spanning across all domestic mammals, which are not found in their wild ancestors or counterparts (Darwin, 1868) (Wilkins, et al., 2014).

Today this combination of traits can be collectively referred to as "domestication syndrome". The term includes characteristics such as increased docility and tameness, changes in coat colour and structure, alterations in body size, changes in ear and tail morphology, reduced tooth size, craniofacial morphological changes, and changes in the reproductive cycle. Researchers have also found domesticated animals to have an increased window for socialisation, which has been linked to changes in plasma corticosteroid levels. This indicates that the process of domestication, meaning strong selection based solely on friendliness towards humans, leads to changes in physiological and hormonal mechanisms that are again linked to social behaviour (Trut, 1999) (Wilkins, et al., 2014).

Trait	Animal Species
Depigmentation/piebaldism	All
Appearance of dwarf and giant varieties	All
Floppy ears	Rabbit, dog, fox, pig, sheep, goat, cattle, and donkey
Reduced ears	Rat, dog, cat, ferret, camel, alpaca
Shorter muzzles	Mouse, dog, cat, fox, pig, sheep, goat, and cattle
Smaller teeth	Mouse, dog, and pig
Docility	All domesticated species
Smaller brain or cranial capacity	Rat, guinea pig, gerbil, rabbit, pig, sheep, goat, cattle, llama, camel, horse, donkey, ferret, cat, dog, and mink
Reproductive cycles (more frequent oestrus cycles)	All except sheep
Juvenile behaviour retention in adults	Mouse, dog, fox, and bonobo
Curly tails	Dog, fox, and pig
Shortened tails, fewer vertebrae	Dogs, cats, sheep, Arabian horse

Figure 2 Table describing some of the most common traits found to be modified in domestic animals when compared to those found naturally in the corresponding presumed wild ancestors. This is a redrawn, modified version inspired from the table shown in a 2014 study on Domestication syndrome in mammals (Wilkins, et al., 2014) and Trut's study on the domestication process of canids (Trut, 1999).

Aggression as a trait and its links to other behaviours

1.1 Fearfulness, anxiety, and aggression

It is easy to imagine that fear and aggression are linked behaviours, with one often leading to the other. This is supported by studies surveying both behaviours, usually through statistical analysis of owner questionnaires such as the C-BARQ. In some studies researchers choose to focus on a trait they call "boldness", or the lack of fear, rather than fearfulness. There are also different subcategories of fear and aggression, as an aggressive individual obviously is not necessarily aggressive in all situations. The commonly examined sub-categories for research on aggressive behaviours seem to include owner-directed aggression, stranger-directed aggression, dog-directed aggression (meaning aggression towards strange dogs), and dog rivalry (meaning aggression towards dogs from the same household). As aggression is associated with fear, stranger-directed fear (against unknown humans) and dog-directed fear (against unfamiliar dogs) are examples of traits which may also be included in research into aggression (Duffy, et al., 2008) (Zapata, et al., 2016) (Zapata, et al., 2020).

A 2017 study looking into risk factors for stranger-directed aggression (SDA) found that a reported fear of strangers was strongly associated with aggression directed towards strangers (Flint, et al., 2017).

1.2 Direction of aggression

Aggression is often categorised based on how and where it is directed. Some dogs will be aggressive towards dogs only, some only towards humans. Some will be aggressive towards both, but only in case of strangers. Some are seemingly not aggressive towards humans or dogs but will show aggression directed towards their owner or rivalry around other dogs in the same household.

A 2008 study looking at behavioural statistics in connection to breeds found that some breeds will have higher scores towards specific targets. Examples of this would be Akita Inu and Pit Bull Terriers scoring higher than other breeds on dog-directed aggression, which makes sense when you take into consideration that both breeds have a history of being used for dogfighting. Other breeds show generalised aggression, such as Chihuahuas and Dachshunds. This in itself is an interesting observation, as we will see in the chapters discussing potential genetic factors linking aggression and morphology. Other breeds, such as Whippets, Greyhounds and Retrievers among others, had lower than average scores for aggression toward both humans and other dogs. English Springer Spaniels were found to have increased aggression levels in the case of conformation-bred individuals, when compared to working lines. The opposite was found for the Labrador Retriever, where show-bred individuals were less aggressive towards their owners than their field-bred counterparts (Duffy, et al., 2008).

In a study attempting to map the genetics behind canine fear and aggression, Zapata et al. found that the traits for stranger-oriented fear, stranger-directed aggression and dog-directed aggression appeared clustered in every data set. However, the owner-directed aggression did not cluster with the other traits, possibly suggesting that the former could be genetically related whilst the latter is the result of a different genetic background (Zapata, et al., 2016). This could be supported by the finding of a Taiwanese observational study which hypothesised that aggression towards owners might be regulated differently from stranger-directed aggression and aggression towards other dogs (Hsu & Sun, 2010).

1.3 Aggression as a wanted behaviour

Certain dog breeds are unique in that they have been bred specifically for aggression for centuries. Most likely this is a recent phenomenon, as attempting to domesticate a canine whilst also keeping high levels of fear and aggression seem counterproductive.

Several breeds are known for their aggressive behaviour, although common for all of them is the fact that these traits are wanted and desired by humans. Large guardian dogs (LGD) are famously loyal towards what they perceive as their own pack and many breeds will happily co-exist with humans and all sorts of livestock but will show aggression and fight any new arrival on their territory, be that human or animal.

Pit bull breeds were traditionally bred for dog fighting, where they would fight until death for entertainment purposes and often sustain serious injuries. As a consequence of this, their attitude towards humans had to be extremely forgiving in order to allow owners to remove a sometimes seriously hurt animal from the fighting pit, and nurse it back to health without sustaining bite injuries from the pained animal.

Still today many driven working breeds are expected to have a certain level of controllable aggression in order to function for their intended use. Working police dogs are an example of this, as they are required to show controlled aggression towards any individual their handler directs them towards. Police work requires the dog to attack with extreme intensity, ferocity, and boldness, but also the ability to stay in control of their actions and be able to let go the moment they are released from their command.

1.4 Pathological rage

In certain breeds, mostly spaniels, a different type of aggression is described. Sometimes referred to as "rage syndrome" or "spaniel rage" in everyday language, this condition is not well-understood but is widely described anecdotally. Owners describe dogs which have previously had no issues with aggression go suddenly "mad" with rage, to the point where the owner is unable to contact the dog and sometimes fear for their own life. The events seem to present as "episodes" with the dog suddenly deviating in and out of the aggressive state of mind, seemingly with no recollection of the episode afterwards. The fact that this appears to be most often observed in specific breeds like the Cocker spaniel and the Springer spaniel could point to some genetic, or at least inheritable, background (Podberscek & Serpell, 1996). The seizure-like state the dogs seem to enter while in the aggressive state could suggest that rage syndrome is some sort of neurological or epileptic disease, most likely thought to be originating in the temporal lobe (Chandler, 2006). However, the seriousness of the situation and the fact that the episodes are rare and of sudden onset likely mean that many dogs are euthanised rather than treated or studied. Despite this, smaller studies do exist where dogs appear to have responded well to anticonvulsant treatment (Dodman, et al., 1992).

Materials and methods

1.5 Obtaining materials

Materials for this literary review have been obtained using scientific search engines such as Google Scholar and PubMed. The main focus has revolved around studies seeking to explain aggression through the discovery of specific genetic backgrounds, and correlations between aggressive behaviour, genomes and phenotypes.

Due to the technology used in genetic research, including genome mapping, being relatively recent, I have chosen to give a special emphasis to genetic studies created in more recent years. Largely meaning from 2011 until 2021 (present). However, to provide a thorough background for the recent discoveries I have also chosen to include older, fundamental studies concerning the process of evolution and the impact of selection pressure and genetics on physical and psychological traits.

1.6 Methods used during research

Behaviour, and subsequently behavioural aggression, is a difficult area to isolate for research. As was already established, behaviour is a complex trait rooted in both hereditary genetics and environmental factors. Therefore, several approaches can be taken by researchers attempting to study behaviour. The most used methods will be described below. I will also attempt to elucidate potential shortcomings and strengths for each approach.

1.6.1 Live animal experiments

For instance, experiments where researchers attempt to simulate domestication through the rearing of several generations of animals under heavy selection pressure. Or the rearing of litters under laboratory conditions to examine variations on a breed, family, or individual level when raised under equal conditions. Negative aspects of these experiments are the fact that they often require extreme amounts of time and effort before data can be obtained. Consequently, this can lead to small sample numbers. A positive aspect is the fact that researchers will have first-hand access to the data without having to rely on the interpretations (and potential biases) of others. Perhaps the most famous example of a live animal experiment is the Russian farm-fox experiment, which will be discussed in closer detail later in this review.

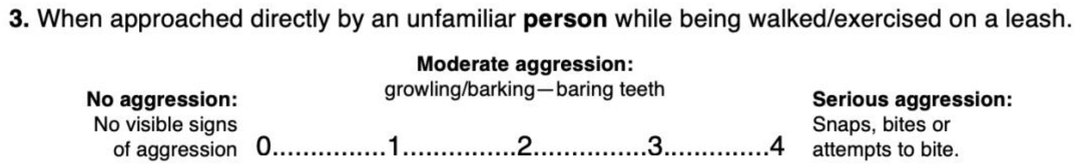
1.6.2 Standardised behavioural tests

There are a multitude of ways to approach a behavioural test, and they can be varied to a great degree depending on the level of standardisation. The goal of the standardised behavioural test is to subject an animal to a standardised stimulus which will elicit a behavioural response. The individual's response can then be compared to the response of other individuals subjected to that same test. The results can be useful to get a general idea of temperament and capabilities. In Scandinavia these tests are commonly used in breeding programmes, both for excluding individuals displaying unwanted behaviours from the breeding group and to promote the use of individuals showing a wanted situational response. They are also used to aid the selection of dogs used for guide dog training and police work in most countries world-wide. However, results obtained from standardised behavioural tests may be open to interpretation depending on who is evaluating the test. They will also show the dog's response at that point in time only, which could be highly dependent on the dog's state of mind on the given day. In animals raised outside of a standardised laboratory environment it could prove difficult to separate learned and inherited responses. There is also risk of the results being influenced by the environment, if the test is not fully standardised and conducted in an entirely controlled setting, and not least by the owner/handler of the dog during the test.

1.6.3 Owner questionnaire

Owner questionnaires are commonly used in behavioural research regarding domestic pet animals. Advantages include the fact that it can drastically widen the subject pool and ease of obtaining data, since subjects do not need to be under the care of researchers. Another advantage is the fact that pet owners tend to spend more time with and develop a deeper bond to their pets than researchers can in a facility, thus getting a more accurate impression of their normal behaviours. However, this can also give rise to problems with owner bias and thus the submission of inaccurate data can be an issue. Moreover, not all owners may be equipped to understand the behaviours they observe and are consequently at risk of misunderstanding their pets and accidentally submitting faulty answers. These errors can be counteracted to a certain degree by meticulously designing the questionnaire in a way which lets the data be submitted as objectively as possible by the owners, without them having to draw their own conclusions before answering.

A well-known dog behavioural questionnaire is the standardised C-BARQ (Canine Behavioural Assessment and Research Questionnaire). It was developed by James A. Serpell at the University of Pennsylvania for the specific goal of being able to accurately assess behavioural and temperamental traits in pet dogs. It does this by asking respondents to describe their dogs' typical responses to specific events on a 5-point scale (Figure 3). The scale describes the frequency or intensity of the behaviour depending on what category the behaviour falls under. The general C-BARQ categories are sociability, trainability, aggression, fear and anxiety, excitability, separation-related behaviour, attachment- and attention-seeking behaviour, and miscellaneous (Serpell & Hsu, 2003).


3. When approached directly by an unfamiliar **person** while being walked/exercised on a leash.

No aggression: No visible signs of aggression 0..............1..............2..............3.............4 **Serious aggression:** Snaps, bites or attempts to bite.

Moderate aggression: growling/barking—baring teeth

Figure 3 Example of a question from the Canine Behavioural Assessment & Research Questionnaire (C-BARQ) showcasing the scale system from 0 (not aggressive) to 4 (serious aggression) to allow an owner to rate their dog's level of aggression. *Picture source* (Serpell, u.d.)

1.6.4 Expert questionnaire

Researchers sometimes chose to utilise field experts, rather than owners, when collecting data through questionnaires. In the case of dogs, relevant participants may be dog trainers, veterinarians, trial judges or breeders. These people regularly interact with a multitude of dogs and may be more likely to remain objective compared to an owner. However, there is still a risk of personal opinion or breed prejudice influencing the validity of their answers. Additionally, for professions such as veterinarians the individual's knowledge and interest on the subject of dogs and stereotypical breed behaviours may vary greatly depending on the personal interests and work experiences of that individual.

1.6.5 Genome-Wide Association Studies

Genome-Wide Association studies, or GWA's, simply map the genomes of individuals and compare the results. They can be applied to individuals within a breed, group, species or even across species. However, the results in themselves are open to interpretation as they are only able to show potential correlation, not causation. Because this method is so low in specificity, it is usually applied as a secondary method after an initial screening using methods such as owner questionnaires.

Phenotypic correlations

Many studies aim to explore the relations between animal morphology and behaviour. As the concept of "domestication syndrome" (DS) demonstrates, the two topics are seemingly intimately linked, and it is difficult to avoid the matter of morphology when discussing genetic backgrounds for behaviour in domestic animals.

The mere existence of a "domestication syndrome", and the fact that these same traits are applicable to every species of domestic animal, is suggestive of the existence of a link between domestic behaviours and domestic morphology. This theory has been strengthened through studies aiming to recreate the domestication process, most notably the Russian Farm-Fox experiment which started in the late 1950's and is still ongoing today. Geneticist Dmitri Belyaev and his team of Russian scientists obtained a group of 130 largely undomesticated silver foxes from fur farms and used these foxes to start a breeding programme. They selected for only one thing: friendliness towards humans, or lack of fear and aggression. The resulting pups were tested rigorously and classified based on degree of tameness, with only the friendliest individuals being allowed to continue in the breeding programme. Care was taken to avoid inbreeding and maintain genetic diversity within the group. Results quickly became apparent; already in the 6th generation the scientists found they needed to add a new "elite" class to their classification system, as the pups were reaching new levels of eagerness towards human contact. Interestingly, what followed these behaviours closely was the appearance of new morphological traits. Already at the 8th to 10th generations depigmentation was seen, specifically white spots in the facial region. What followed was the appearance of floppy ears, rolled tails, and changes in skull ratios. In later generations, traits such as short leggedness, as well as under- and overbites were seen. These were less frequent, but still many times more likely to appear in the domestic population than in other groups. Moreover, a number of these new traits turned out to be dominant, meaning the mutation is decisively not a result of accidental recessive inheritance within the breeding group (Trut, 1999) (Wilkins, et al., 2014) (Wang, et al., 2018).

The findings lead scientists to believe that there is a considerable correlation between tameness, or lack of aggression, and morphology (Trut, 1999). The most widely accepted explanation for this phenomenon is the theory that behaviour is a quantitative trait diffusely regulated by several genes: a polygenetic trait (Ilska, et al., 2017). A fox can have high level of aggression, low aggression, or be somewhere in the middle of these extremes. The fact that other, seemingly unrelated, traits such as the presence of white spots or floppy ears appear when we select for certain behavioural traits can be indicative of these polygenes being fairly high on the genetic hierarchy. These are examples of morphological traits which are consistently found across all domestic species, possibly alluding to the fact that they are pleiotropic in nature (Wilkins, et al., 2014). Even further support for the pleiotropic theory can be lent from the fact that other changes in the foxes' neurochemical and hormonal systems followed the newfound behavioural and morphological deviations (Trut, 1999).

Studies have been made on a variety of traits found in domestic dogs and the possibility of them being linked to behaviour, with various results. Some of these will be discussed below. Notably, the traits connected to domestication syndrome is present in the modern dog to the highest degree, evident from the wide variety of features found in our current canines. The early domestic dog appears to have followed the pattern of decreased size and paedomorphic features when compared to its predecessor, the wolf (Morey, 1994). However, many of our modern breeds have in very recent times been purposefully bred using artificial selection for specific exteriors. This likely diverges from the original selection process, based predominantly upon human compatibility (Wang, et al., 2016), and thus artificially remoulded the modern dog from its original shape (Morey, 1994). This can likely present complications for the results of genetic investigations based on current morphology, as the modern exterior doesn't necessarily correlate with archaic features of the breeds and individuals examined. A better model might have been the early domestic dog, with an exterior which might have reflected his behavioural properties better than the modern-day show dog and family pet. (Zapata, et al., 2016)

1.7 Body size and mass

Researchers examining the domestication of mammalian species have observed that the shift in selection pressure tends to lead to diminished body size (Tchernov & Horwitz, 1991). Many theories exist as to why this occurs, most linking it to increased reproduction rate and lowered age of maturation, shortening the generation time. This shift in size appears to be relevant also to the domestic dog. Early specimens of dogs frequently show crowded and overlapping teeth, seemingly as a result of rapid size reduction (Morey, 1994). The smaller size could also present an advantage with the shift in diet, as dogs evolved to share their food with humans as opposed to having to take down large prey themselves.

In Belyaev's domesticated fox population shifts in body composition could be seen, as well as changes in the reproductive cycle. The observed alterations in both traits were much more modest than the changes present in our modern dogs but could support the theory that the two are connected. The Russian scientists originally believed they would be able to select for foxes who could breed year-round, similarly to dogs. However, this was not the case, as only minor increases in the reproductive rate were observed. Domesticated foxes reached sexual maturity a month earlier than the non-domesticated group and had litters on average one pup larger (Trut, 1999).

Zooarcheologist Darcy F. Morey compared the skulls of early domestic dogs to those of juvenile wolves and found striking resemblances, much more so than with the adult wolves. He suggests that the domestication process of the dog altered the developmental programme in such a way that while the dog reaches sexual maturity faster than its wolf counterparts, other aspects of his development is slowed down (Morey, 1994). Supporting this hypothesis is the research of zoologist Robert K. Wayne, who found that domestic dogs and grey wolves are extremely closely related, differing only through small changes in developmental rate and timing (Wayne, 1993).

Modern studies on dogs exploring the relationship between behaviour, body mass and size have found small body size to strongly correlate with aggressive and undesirable behaviours (McGreevy, et al., 2013) (Zapata, et al., 2016) (Stone, et al., 2016). They also found shorter dogs to be more aggressive towards both owners and strangers (McGreevy, et al., 2013) (Stone, et al., 2016).

These findings can be interpreted in several ways. For instance, the modern miniature dogs and their behaviours are likely influenced by a variety of factors, most notably human selection, and milieu. In a 2013 study McGreevy et al. raises the notion that humans may be more tolerant towards undesirable behaviours in small dogs and may therefore be more likely to relax the selection against these behaviours in small dogs, whilst being more likely to select against them in larger dogs. The higher rates of problematic behaviours in small dogs could also be due to the way they are treated as a result of their small size, or the personality of the typical owner of small versus large dogs (McGreevy, et al., 2013).

A newer study from 2016 aimed to bring more clarity to these questions by exploring the genetic background and possible behavioural ramifications of decreased size through genetic mapping using GWA (Zapata, et al., 2016). Several associations were found, which will be discussed in a subsequent chapter of this review.

1.8 Ear and tail morphology

The outward effect of traits such as ear and tail shapes has long been recognised (Figures 4 & 5). This phenomenon is evident in breeds created specifically for intimidation, like the Dobermann, and for lapdogs like the spaniels. It is no coincidence that the former was traditionally kept in a tight ear crop, whilst the long, silky ears of the latter were used to emit a soft, good-natured personality even by Walt Disney. This also became clear when a 2015 study asked participants to rate the perceived personality of dogs based solely on photographs. Dogs with floppy ears were rated as perceived significantly higher in traits such as Agreeableness and Emotional stability compared to the pointy-eared dogs (Fratkin & Baker, 2013).

Belyaev's domestic foxes also showed increasing likelihood of being born with floppy ears as the level of domestication increased in the later generations, as well as with a wider variety of tail morphologies (Trut, 1999). It is interesting to note that most, if not all, wild canids have upright ears whilst the domestic dog comes in a variety of ear shapes. It is one of the traits that make up "domestication syndrome" with even Darwin remarking upon the occurrence of "droopy ears" in domesticated species as early as in 1859 (Darwin, 1859).

A 2011 genetic study found a loci on chromosome 10 where variations were strongly associated with ear shape. The same region also showed strong correspondence with boldness as a personality trait, as well as small body size (Vaysse, et al., 2011).

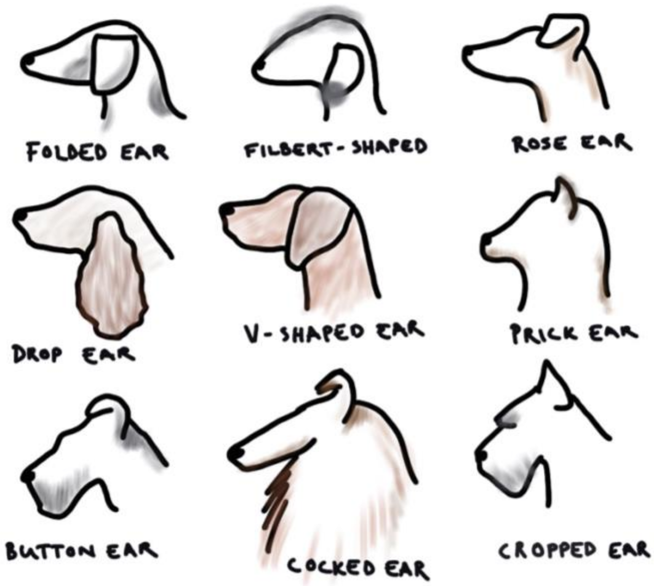


Figure 4 Illustration showing some of the ear shapes found in domestic dogs.

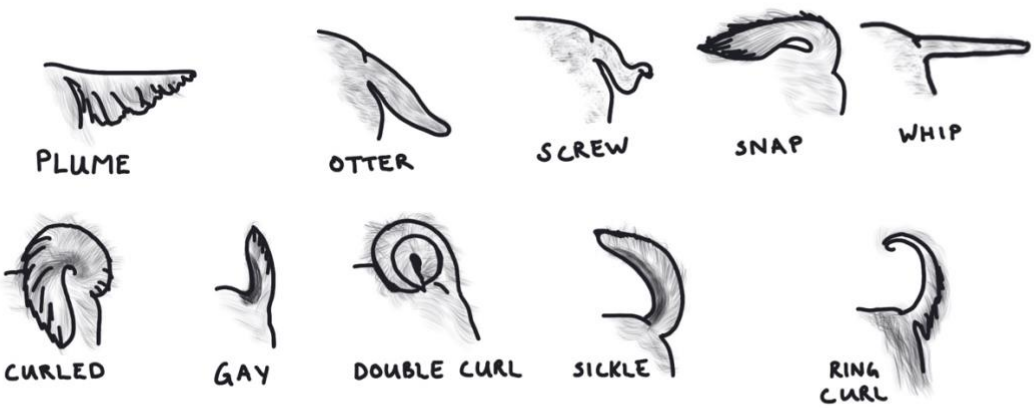


Figure 5 Illustration demonstrating some of the tail shapes found in domestic dogs.

1.9 Skull shape

Skull shape among domestic animals is widely studied and subject to much discussion. In dogs, there is a wide range of skull shapes present with clear patterns related to the different breeds and types of dogs (Figure 6).

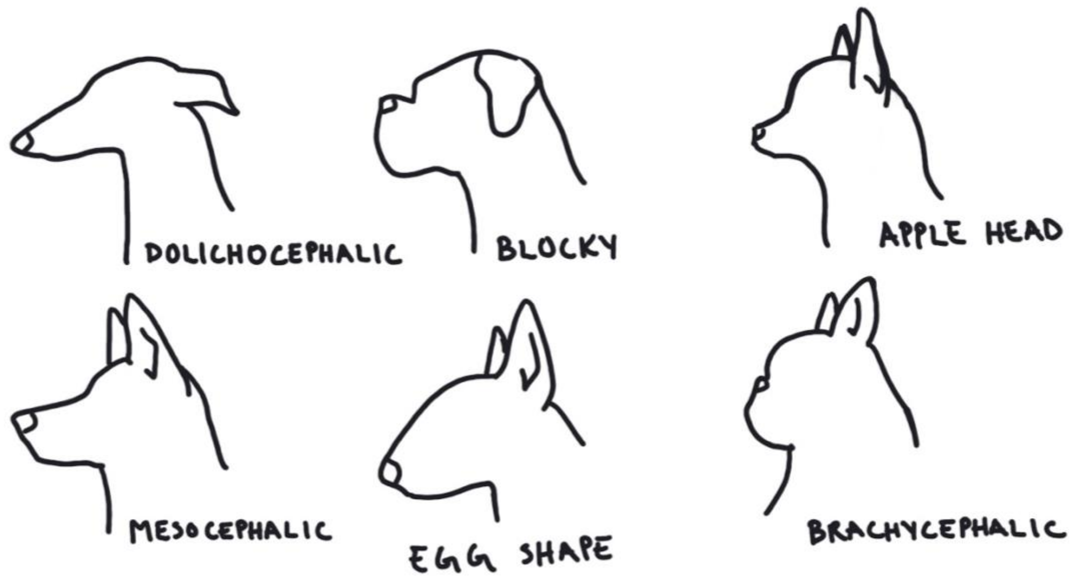


Figure 6 Illustration showing some of the skull shapes found in modern domestic dogs.

A 2016 study explored the relation between morphological traits such as cephalic index (CI: ratio of skull width to skull length) (Figure 7) and behaviour by comparing the morphological data of participating dogs to their Dog Mentality Assessment (DMA). DMA is a behavioural test where the dogs were scored by trained observers as they were presented to 10 subtests designed to evoke a behavioural response. Findings showed clustered differences between responses in brachycephalic (high CI) and dolichocephalic (low CI) breeds. However, clear patterns are difficult to read from tests like the DMA as so many factors can be attributed to the results. For instance, we would expect dolichocephalic breeds to score highly in the trait "chase proneness" as chasing pray is what they have been bred for over thousands of years. Nonetheless, the test results for this trait were surprising with the brachycephalic dogs scoring higher (Stone, et al., 2016). When analysing the test more closely it became clear that the dogs are walking with their handler, who remains passive throughout, while the subtests are performed by unknown people. The chase test is performed by an unknown person inviting the chase or play, which could be off-putting to breeds like sighthounds, developed for independent hunting at a distance. This could lead to inaccurate results, as the simulated situations does not necessarily encourage or appeal to the true potential of every breed. This again points back to the fact that behaviour is a complicated and difficult area of research, influenced by many variables. More tests with several different approaches for each trait examined and a larger subject pool would likely be needed in order to obtain a less ambiguous result.

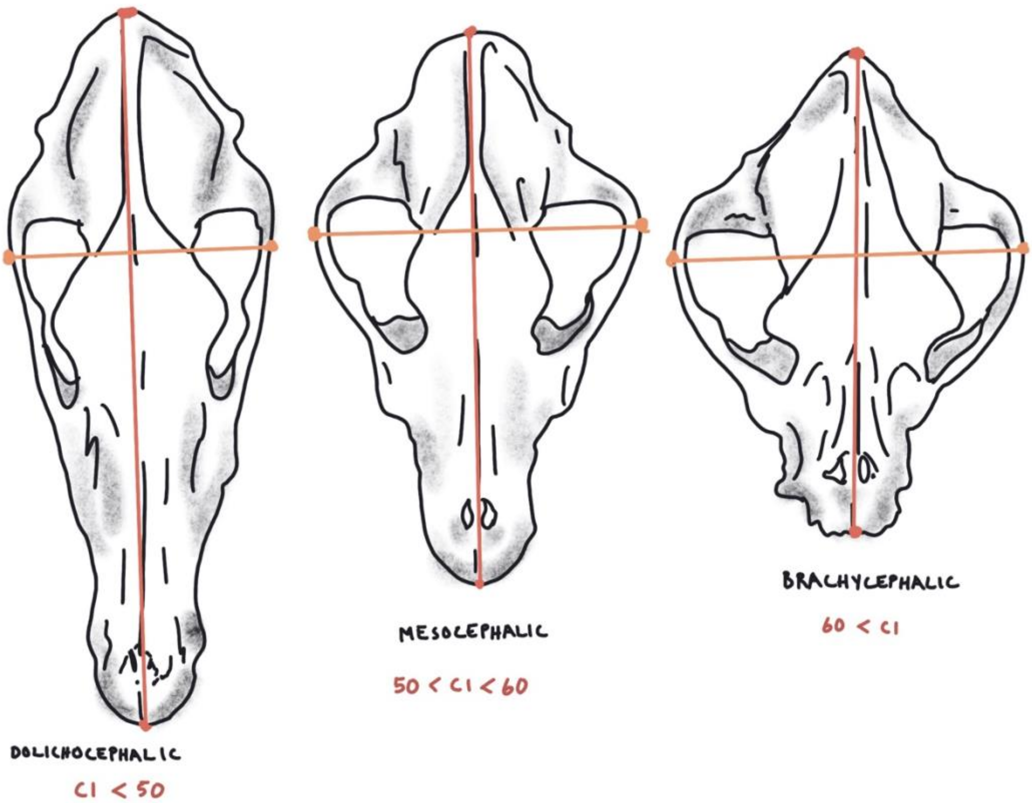


Figure 7 Illustration demonstrating the cephalic index (CI) differences in dolichocephalic, mesocephalic and brachycephalic dogs. CI is the ratio between the skull width, measured from zygomatic arch to zygomatic arch, and skull length, measured from inion to prosthion. In live dogs the length is commonly measured from occiput to the tip of the nose. Dogs are divided into dolichocephalic (long-skulled) breeds, usually dogs bred for chasing and running, mesocephalic (moderate-skulled) and brachycephalic (broad-skulled) breeds, likely bred for increased bite force **(Helton, 2009)**.

1.10 Colour

Several studies have attempted to explore the relationship between colour and behaviour. It appears to be a common narrative, at least within some dog breeds, that differences in colour relate to certain personality traits.

Interestingly, there are some scientific findings that suggest colour could play a role in personality type. Examples of these are surveys made on the infamous English Cocker Spaniel (ESC), a breed where colour stereotypes in connection with bad temper and aggression are common. English Cocker Spaniels of the solid red colour are often said to be more aggressive than their black or piebald peers. A randomly distributed owner questionnaire study of nearly a thousand ECSs from the UK found this to be the case; solid coloured ECSs were significantly more likely to show aggression than the piebalded individuals, and out of the solid colours the red or golden dogs were the most aggressive. (Podberscek & Serpell, 1996)

The study is supported by another, made on ESCs in Spain in 2009. This study analysed the aggressive behaviour of 145 ECSs presented for temperamental problems by comparing them to a group of non-aggressive individuals of the same breed, as well as a group of non-aggressive dogs of different breeds. Interestingly, one of their findings was that the golden, or red, coat colour was overrepresented in the aggressive group. (Amat, et al., 2009)

A 2019 study made on 225 Labrador Retrievers explored the theory that colour bore any significance for disadvantageous personality characteristics within the breed, with breed enthusiasts anecdotally claiming that chocolate Labradors are harder to train and more aggressive than their black or yellow counterparts. Instead, they found the yellow dogs to score considerably higher in familiar dog aggression, although these findings seemed less significant once the data was corrected. (van Rooy & Wade, 2019)

A 2016 study made on cats surveying potential links between behavioural associations and morphological traits found red cats to have the highest level of pray interest, whilst piebalds were found to be the least aggressive towards strangers. (Wilhelmy, et al., 2016)

These findings could be underpinned by the fact that depigmentation, or piebaldism, is indeed one of the traits that make up "domestication syndrome". In Belyaev's silver fox domestication study one of the first changes they noted in their progressively amiable population was the appearance of white patches and an increase in coat colour variety. (Trut, 1999).

A possible explanation for the perceived trend concerning aggression and red individuals could be the fact that melanin shares a common biochemical synthesis pathway with the catecholamines (Podberscek & Serpell, 1996) (Figure 8). Neurochemicals, such as the catecholamines dopamine and norepinephrine, are believed to play key roles in modulating behaviour. This hypothesis could help to explain the recurring perception of red or chestnut animals being perceived as more hot-headed than others across many species, although factors such as linebreeding and bias based in archaic superstitions must also be taken into account.

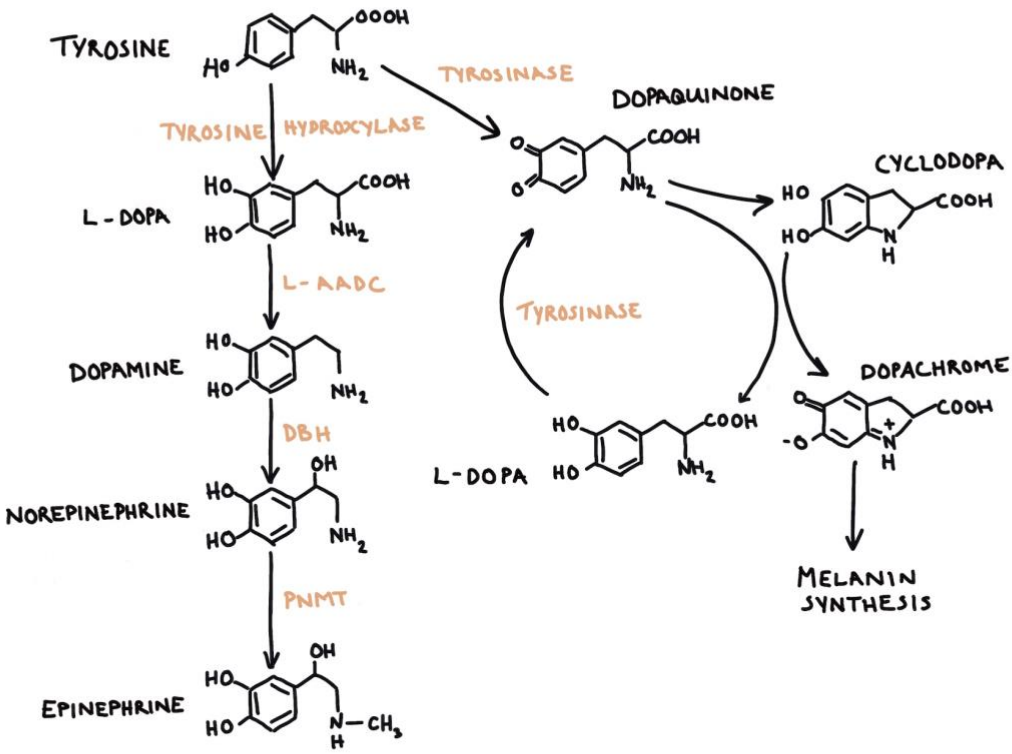


Figure 8 Dopamine synthesis pathway demonstrating how melanin is derived from the same amino acid as several neurotransmitters though to impact behaviour. The figure was created by the author of this thesis, with inspiration from https://www.researchgate.net/figure/Metabolic-pathways-for-catecholamine-synthesis-and-melanin-formation-L-AADC-L-aromatic_fig1_10686351

1.11 Gender

Several studies have found correlation between type and levels of aggression and gender. As in other behavioural questionnaire-based studies, it can be difficult to interpret the data presented in an objective way as it is usually submitted by the owners.

A 1985 study on the characteristics of dogs behind severe attacks on humans found that out of 5711 dog bite reports, only 16 of these incidents met the requirements for "severe" attacks. When examining characteristics of the dogs behind these attacks, 100% of the aggressive dogs were intact males (Wright, 1985). Another study looking at bite incidents in Ireland also found that more than 50% of dogs behind bite incidents were intact males, whilst just over 13% were intact females and 32% of attacking dogs were of unknown gender. The neutered dogs were overwhelmingly outnumbered by the intact dogs in the bite incident statistics, with neutered dogs making up only 3,7% of the cases in total (O'Sullivan, et al., 2008).

However, it must be taken into consideration the fact that there are many forms of aggression. While intact male dogs seem, in these statistical surveys, to be behind a higher number of the severe attacks on humans, those attacks are still a rarity in themselves. It might still be argued that females could be more aggressive overall in comparison to males, although the attacks may be less severe.

A study surveying risk factors associated with stranger-directed aggression (SDA) found that neutered males were at the greatest risk of developing SDA compared to any other group. Males in general were found to be significantly more likely to be severely aggressive (Flint, et al., 2017). However, a 2020 study found social fearfulness to be associated with females (Puurunen, et al., 2020).

There could also be breed differences skewing the statistics, as bites from small dogs are much less likely to have a severe outcome and thus are not likely to become part of the statistic at all. We also need to take into consideration whether the victim of the attack is a stranger entering the dog's territory or a known human posing no threat. Whether there was food involved and whether the dog might have given warning signs before attacking which were not respected are also important factors to consider in order to understand the full situation. Situational details like these can be very difficult to obtain when attempting to survey bite statistics in a representative way.

Physiological correlations

As could be ascertained in Belyaev's farm-fox experiment, changes to the hormonal and neurochemical systems were evident in the domesticated group of foxes. Seeing as neurotransmitters play a role in nearly every bodily function and are the key regulators for functions ranging from mood and concentration to heart rate, breathing and sleep cycles, this finding is mostly to be expected when studying behaviour. For aggression as a trait, the neurotransmitters might hold the key for understanding why some individuals are more aggressive than others. This is especially relevant when we take into consideration the likely existence of rage syndrome and the suggested finding that it can be suppressed through the use of anticonvulsants (Dodman, et al., 1992).

The main neurotransmitters of interest include glutamate, serotonin, and dopamine. These are widely known to heavily impact temper and mood levels. It is important to note that although the impact of neurotransmitters is relatively indisputable, the search for genes behind their effects is demanding, and still not well understood.

Even in the case of discoveries revealing connections between a neurotransmitter and behaviour, it is difficult to pinpoint the genetic background for these results. An increase or decrease in a certain neurotransmitter could be due to changed synthesis of this chemical, a change in its reuptake, or perhaps an altered level of the enzyme controlling its inactivation. It could also be due to alterations in genes which control all these points (Houpt, 2007).

Additionally, hormonal levels of interest include androgens and cortisol levels. Androgens because it is the main hormone regulating male characteristics, and as previously discussed it is believed gender could play a role in predisposition for aggressive behaviour (Flint, et al., 2017). Cortisol levels are interesting for several reasons, amongst them is the aspect that Belyaev found significant changes in the plasma cortisol level of his silver fox population as the domestication process advanced (Trut, 1999).

1.12 Dopamine

Dopamine (DA) has many functions but is mostly talked about in the context of memory, reward, and pleasure. It plays a role in learning and motivation and is also thought to be a key component of habit-formation and addiction. Dopamine is a neuromodulator, and among other roles it also plays a part in the adrenal stress response as a catecholamine along with epinephrine and norepinephrine. It is a relatively common veterinary drug target, as dopamine antagonists are known to cause sedative effects and relaxation. Acepromazine is an example of a dopamine antagonist used in veterinary medicine to evoke relaxation (Houpt, 2007).

In a 2018 study, researchers found that dopamine plays a part in lessening fearful reactions over time through a brain circuit known as ventral tegmental area (VTA)-dopamine system (Luo, et al., 2018). This could play a big part in understanding how we overcome fear and in unlearning fearful associations.

A 2010 study made on aggression in dogs in connections with neurotransmitters identified potential links between dopamine and serotonin levels and human-directed aggression. However, researchers were unable to pinpoint a genetic cause suggesting that the inheritance of aggression is complex (Våge, et al., 2010).

One 2013 study found that a dopamine transporter gene *SLC6A3* was associated with behavioural changes in Belgian Malinois dogs. A nucleotide insertion *PolyA(22)* in this gene was associated episodic biting behaviours and seizures through owner reports. The researchers were unable to draw any definite conclusions due to the complex polygenic nature of behaviour, but the results did not rule out the effect of *SLC6A3* (Lit, et al., 2013).

1.13 Serotonin

Serotonin, or 5-hydroxytryptamine (5-HT), plays an important role in the central nervous system. It is an inhibitory neurotransmitter which affects many bodily processes and is heavily linked to mood and mental state. It also plays a part in circadian rhythm, appetite regulation and sexual function. Low levels of serotonin are associated with depression and poor memory, whilst normal levels help produce feelings of contentment and happiness (Jenkins, et al., 2016) (Wang, et al., 2018).

A 2018 study exploring the genomic responses to selection for tame and aggressive behaviours in silver foxes found several genes involved in key pathways for neurological processing, including the serotonin receptor pathway, to be differently expressed in the tame and aggressive populations. Various differences were found both in the serotonin receptor genes and downstream signalling genes, with nearly all the changes found were in the direction of increasing serotonin signalling in the tame group of foxes (Wang, et al., 2018).

A 2010 study on aggressive dogs also found significantly lower blood serum serotonin levels in aggressive dogs compared to non-aggressive individuals, with the lowest levels in those dogs showing defensive, possibly alluding to fear-based, aggression (Rosado, et al., 2010).

Serotonin is a neurotransmitter which is highly topical in the context of aggressive behaviours. A nonsensical mutation in the monoamide-oxidase-A (MOA-A) gene on the X chromosome has been linked to aggressive and impulsive behaviour in humans, as well as mice and rats. MOA-A catalyses the metabolic breakdown of serotonin, norepinephrine, and dopamine, meaning MOA-A knockouts have increased levels of serotonin. However, MOA-A inhibitors given to adults with the normal MOA-A gene has not been shown to increase aggression and is used as an antidepressant. This is theorised to be because of dysregulation of the serotonergic brain circuits during foetal development as a consequence of the increased 5-HT levels (Tricklebank & Petrinovic, 2019).

1.14 Glutamate

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system and represents a crossroads between various metabolic pathways. It is the most abundant free amino acid found in the brain, present in nearly all brain synapses and therefore essential for normal brain function.

Glutamate has been linked to episodical violence and is suspected of playing a role in rage syndrome. These violent episodes are thought to share a common mechanism, namely glutamatergic activity in the temporal lobe. However, this type of behavioural pathology is relatively rare and so the research is limited (Miczek & Fish, 2005).

In canine domestication, changes in glutamate receptor genes GRIA1 and GRIA2 are believed to have played a part in the psychological and behavioural modifications needed for dogs to thrive in a human environment (Wang, et al., 2016).

There are few studies exploring the genetic background in glutamate changes in canines specifically, but also in this area of research the silver fox projects have made interesting discoveries. A 2018 study found that several receptor and signalling genes differed between tame and aggressive individuals, with the tame animals having significant up-regulation of the downstream signalling genes. The glutamate pathways involved are thought to play a role in fear conditioning, and so these findings might be consistent with a more docile response to human handlers. These results could support the theory that the genetics behind neurotransmitters and their pathways might play a key role in the aggressive behaviour of animals, but more research is needed on the mapping of specific genomes in order to pinpoint clear connections (Wang, et al., 2018).

1.15 Epinephrine and Norepinephrine

These catecholamines are most widely associated with the fight or flight response and are released in the body's response to stress. Norepinephrine is produced from dopamine by dopa-decarboxylase, meaning these two neurotransmitters are closely connected. Epinephrine is a norepinephrine analogue compound formed by N-methylation. Their release is carefully balanced through the noradrenergic receptors, which are divided into α- and β-subtypes, each with further subtypes (Figure 9). Since the noradrenergic system is so prevalent in the brain and also so closely linked to the other neurotransmitters, a change in any of these is likely to have add-on-effects affecting the noradrenergic system.

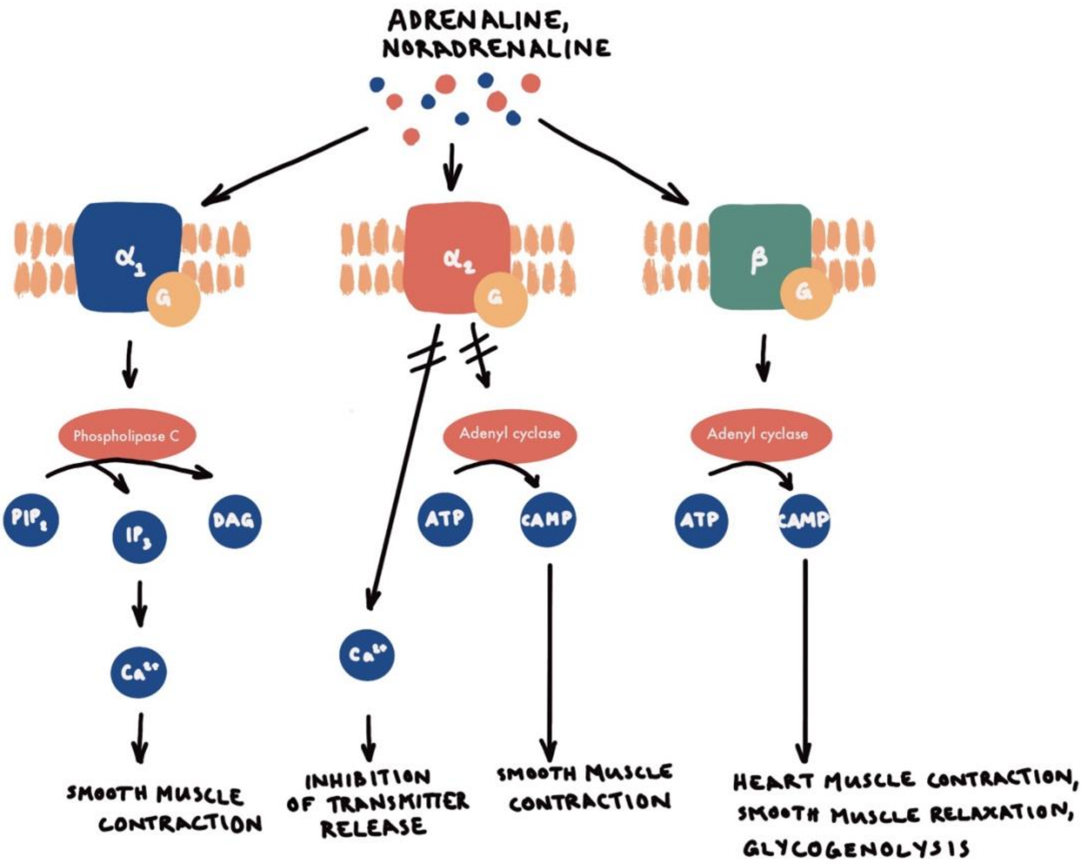


Figure 9 Noradrenergic receptor system and their mechanisms. α-1, α-2 and β adrenoceptors couple to G-proteins resulting in a wide range of reactions in various parts of the body depending on what pathway is stimulated. This figure is redrawn and inspired by an existing figure available at https://en.wikipedia.org/wiki/Adrenergic_receptor

High levels of norepinephrine release are associated with aggression in both humans and animals (Torda, 1976) (Gerra, et al., 1997).

A new study analysing a polymorphism in the canine beta-hydroxylase gene (DBH) of 110 dogs of different breeds found significant differences in allele frequencies between the aggressive and non-aggressive dogs, indicating that the DBH gene is a promising candidate for canine behavioural studies (Polasik, et al., 2021).

1.16 Androgens

Androgens are steroid hormones which regulate male characteristics and play an important role in sexual dimorphism. Seeing as there are studies suggesting a connection between gender and certain forms of aggression, androgens seem a fairly obvious candidate when considering aggressive behaviour (Flint, et al., 2017). However, not many studies have been made on the genetic connection between androgens and aggressive behaviours in dogs.

One 2011 study exploring this relationship in Akita Inu dogs did find that aggression levels in the male dogs had a connection to the length of the polymorphic trinucleotide repeat region coding for glutamine in the androgen receptor (AR) gene. Males with a shorter allele had higher AR function and increased aggressiveness compared to male dogs with longer alleles. No such connection was found in the female dogs (Akitsugu, et al., 2011).

Although research on the genetic basis and correlations between androgens and aggression in dogs seems to be limited, studies in both rodents (Munley, et al., 2018) (Haug, et al., 1986) and humans (Fuxjager, et al., 2017) show correlations between androgen levels and aggression. However, mapping the specific genetic background of these findings may still be some time away.

1.17 Cortisol

Cortisol is an adrenal stress hormone derived from glucocorticoids. It impacts a wide variety of processes in the body, but generally helps put the animal into a "state of emergency" by driving gluconeogenesis as well as suppressing any functions deemed unnecessary at the time of the critical event (Wingfield, et al., 1998).

Lyudmila Trut and her team found that the delayed development of the fear response and increased length of the socialisation window in their domesticated fox population was associated with a delayed surge in plasma corticosteroid levels (Trut, 1999).

A 2010 study made on aggressive dogs and the hypothalamic-pituitary-adrenal (HPA) axis system found that aggressive individuals had significantly higher plasma concentrations of cortisol compared to the non-aggressive dogs (Rosado, et al., 2010).

Genome-Wide Association Scans

1.18 Candidate genes

As has already been established, GWA can be a very useful tool to uncover genetic patterns. If these can be linked to specific traits, it is a powerful way to drive genetic research forwards. It can be challenging to see connections between genetic patterns and complex traits such as behaviours, as the amount of data gathered in a GWA is enormous. Nevertheless, the use of dog models already provides us with a big simplification from the extremely complicated world of human genetics.

By using GWA in combination with behavioural mapping through questionnaires, scientists have been able to survey large groups of individuals. Through this work several areas of interest have been discovered. However is must be noted that these areas of interest are still diffuse and the findings difficult to interpret, with genomes generally showing large variations between the different breeds and populations of dogs. Foxes are relatively frequently used as genetic models for canids in order to provide a better basic framework for investigations with less genetic stratification present.

Mainly, regions of interest relating directly to aggressive behaviour in dogs have been found on chromosome 18 and chromosome X (Zapata, et al., 2016). Further research found correlations between behaviour and markers on a wider range of chromosomes; namely chromosome 10, 18, 24, 32 and X (Zapata, et al., 2020). There are also mapping studies on fox behaviour where connections have been made between aggression and QLT peaks on chromosome 12 (Wang, et al., 2018) (Nelson, et al., 2017).

1.19 Major genes

A 2020 study attempted to further the use of GWA in connection with canine aggression by targeting a subset of previously discovered GWA loci in both pedigree and mixed breed dogs while including a widened range of investigated behavioural traits. The group built on the knowledge obtained from a previous 2016 mapping study and looked for SNPs at 20 markers which were associated with problem behaviours (Zapata, et al., 2016). They detected correlations between markers on different chromosomes (notably chromosome 10, 18, 24, 32 and X), likely due to genetic stratification in connection with breed development but also possibly related to the early domestication process. Very few correlated markers could be consistently linked to the same traits across dogs from different breeds and crosses, but small body size had a consistent association with problematic behaviour (Zapata, et al., 2020).

The small body size could possibly be used as a relatively good predictor in association with problem behaviours but displays the persistent lack of accuracy when it comes to pinpointing the genetics and morphology behind behaviour. Additionally, the study found a marker on chromosome 10 associated with a diagnosis of aggression. This may be a useful region of interest for future studies on the subject and expands on our existing knowledge of genome scans and their relation to behaviour. However, more research seems to be needed on the area as a whole before more decisive conclusions can be drawn.

Conclusion

Aggression is a complex trait influenced by many factors. Environment, upbringing, and training certainly plays a significant role, but likely so does genetics. This has in many ways been proven through the successful emergence of domestic animals artificially selected and bred form wild counterparts with specific behaviours in mind. Behaviours are highly nuanced and often difficult to categorise in clear ways compared to many of the traits associated with morphology or disease.

Certain behavioural trends can be seen in connection to morphological traits in dogs, likely because of the way we categorised and bred them for specific functions. Whether the association is primarily because the exterior facilitates for the behaviour, or because line breeding focusing on other factors accidentally yielded this specific exterior remains largely unclear.

The most promising genes linking exterior and behaviour are related to size, body mass, skull shape, and ear shape. However, there are stark differences in the different dog breed genomes and few uniform findings have been ascertained in this area thus far.

More promising are the genetics behind neurotransmitters and hormonal systems, which can likely help to explain some of the more extreme, or pathological, variations in behaviour. Dopamine, serotonin, glutamate, and norepinephrine all seem to play important roles in eliciting and controlling aggressive behaviours, but the full extent of their effects and integrations remains elusive. The genetics behind these changes are made extremely complicated by the fact that the neurotransmitter systems are highly integrated to each other and affect such a large scope of bodily processes. However, one research group has already made connections between idiopathic aggression and polymorphisms in the dopamine transporter gene SLC6A3.

Research made on this area could possibly prove applicable also to humans and beneficial for human research as well.

Behaviours such as aggressive tendencies appear to be polygenetic traits, implicating that the way of inheritance and individual expression is complex. As our scientific knowledge in a variety of relevant areas deepen, we are likely to be able to illuminate more of the genetic backdrop for behaviour. For now, we can see more or less relevant trends by using GWA, but the amount of data gathered through these surveys is enormous and results so far have proven largely unpredictable and difficult to replicate across populations and breeds.

Much is still to be discovered when it comes to understanding the true causes of behavioural anomalies. Breeders still need to consider parental temperament in order to have the highest chance of producing mentally stable, sound dogs. Behavioural testing is likely to be useful but ought to be weighed against other factors and the desired capabilities of the breed must be kept in mind. Genetic testing might prove more useful in this area in the near future as the knowledge in this scientific field continues to deepen.

Summary

Aggression and undesirable behaviours are traits still too complex for genome scans to display their full potential in this field. We do not yet have the necessary knowledge to fully elucidate the underlying genetics behind the many allelic variations detected using GWA, and the variables remain too many for us, at this point in time, to correctly and accurately predict exactly which genes are associated with specific behaviours. Aggression in itself, with its many variants and causes, is not completely understood on a biological and physiological level. This makes the approach to selecting the correct candidate genes and regions of interest difficult. Many hypotheses regarding the background and biological mechanisms behind aggression exist, and researchers are helped by the continuous use of GWAs and QTL mapping in order to identify new regions of interest.

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Appendix 4.

Supervisor's certification

I hereby confirm that I am familiar with the content of the thesis entitled

„Genetics of Aggressive Behaviour in Dogs"

Written by **Nora Amdal Valen**
(Student name)

Which I deem suitable for submission and defence.

Date: Budapest, 2021-11-16

Supervisor's name and signature
Dr. Zöldág László Prof. Emer.

Department