Vet Clin Small Anim
33 (2003) 345–363

THE
VETERINARY
CLINICS
Small Animal Practice

Behavior genetics

Yukari Takeuchi, DVM, PhD[a,*],
Katherine A. Houpt, VMD, PhD[b]

[a]*Laboratory of Veterinary Ethology, The University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113–8657, Japan*
[b]*Animal Behavior Clinic, College of Veterinary Medicine, Cornell University, Ithaca, NY, USA*

Human beings have long noticed individuality in animals. To take just the case of companion animals, it is obvious that even within the same species and the same breed, behavior is not homogeneous; individual animals may be excitable, aggressive, docile or nervous. The sum of these behavioral characteristics is called temperament. An understanding of temperament and the biologic background of individual differences not only contributes to the growth of basic neuroscience research but is important within veterinary medicine because of its great significance in our attempt to find an appropriate relationship for coexistence between human beings and animals.

It is still unclear whether individuality is determined by heredity or whether the early environment is more important. As common sayings like ''the child is father of the man'' and ''genius displays itself even in childhood'' indicate, the argument of heredity versus environment has long been a matter of debate. Research in the field of clinical developmental psychology has yielded important results about the influence of the early environment, whereas, the identification of the existence of genes related to temperament in human beings has drawn much attention recently. This article briefly discusses the history of behavioral genetics, concentrating on the study of companion animals, and considers recent research trends.

Classic Mendelian genetic research

The Mendelian laws of heredity were published in 1865 and rediscovered by the beginning of the twentieth century, when they had come to be generally accepted. Researchers began to favor analyzing behavioral

* Corresponding author.
E-mail address: aytake@mail.ecc.u-tokyo.ac.jp (Y. Takeuchi).

PII: S0195-5616(02)00116-X

tendencies that could be explained through these laws. In early research, behavioral tendencies that could be evaluated objectively and easily, such as hunting style and gun shyness in hunting dogs and style of livestock management in herding dogs, were at the center of items for analysis [55]. Among studies concerning temperament, Thorne [2] revealed that excessive shyness in Basset Hounds was caused by dominant genes. Later, Dykman et al [3] developed a nervous strain of pointer, which has been maintained with a normal strain.

The most famous research concerning the temperament of dogs and heredity was that by Scott and Fuller [4], begun in 1945 at the Jackson Laboratory and continuing for 13 years. The results of the research were published as a book in 1965. The main aim of the research was to try to evaluate the heritability of special behavioral traits in various breeds of dog (Basenji, Beagle, American Cocker Spaniel, Shetland Sheep Dog, Wire-Haired Fox Terrier, and crosses between the breeds) by analyzing those behavioral traits in dogs raised in the same environment over generations. When the researchers analyzed their data, they realized that there were great individual differences within a single breed, which could be equivalent to those among breeds, and that a simple Mendelian explanation was impossible. They did find some interesting breed effects. For example, in one study, puppies were weaned at 3 weeks and raised in pairs in isolation. Their only contact with human beings was with one handler who either indulged them (permitted to do anything they wanted with their human handler) or disciplined them (made to sit and stay, come and, later, heel). At 8 weeks, they were tested. The test was preventing the puppies from eating from a dish of meat by slapping them on the rump and shouting ''No!'' and then leaving the puppies alone with the meat. Two breeds, the Shetland Sheep Dogs and the Basenjis, were unaffected by type of handling. The Basenjis, whether disciplined or indulged, ate the meat with a short latency. The Shelties would not eat whether they had been indulged or disciplined. The other two breeds, the Beagles and the Wire-Haired Fox Terriers, differed depending on the way they were handled. The indulged puppies of both breeds took significantly longer to eat the food than the disciplined ones. Later, when placed in a pen with other pups of the same breed, the indulged Beagles were wary and shy. This study indicates the complex relation between nature (breed) and nurture (early handling) [5].

Scott and Fuller [4] also found maternal influence on a puppy's temperament, which was best demonstrated by crossing Basenjis and Cocker Spaniels. When the dam was a Cocker Spaniel and the sire was a Basenji, the puppies were friendly to people, but in the reciprocal cross, where the mother was a Basenji, the puppies were not friendly (Fig. 1). For a more recent observation of maternal effect, see Wilsson [64].

In the 1970s, the object research shifted to working dogs, such as guide dogs and military dogs with a special breeding program. Significant heritability was not discerned among the items of analysis in a large-scale

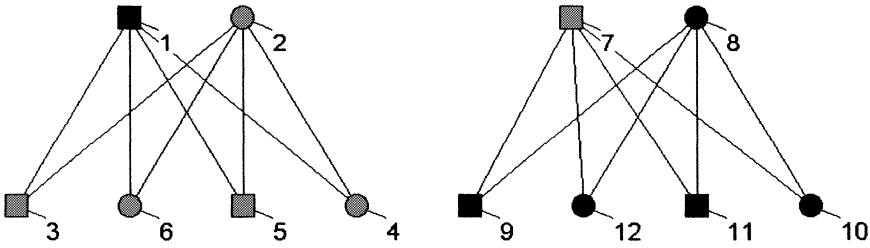

Fig. 1. Maternal effect. Black symbols indicate hostile behavior. Gray symbols indicate friendly behavior. Squares indicate males, and circles indicate females. When a hostile male Basenji (1) is mated with a friendly female Cocker Spaniel (2), the puppies (3–6) are friendly. When a friendly male Cocker Spaniel (7) is mated with a hostile female Basenji (8), the puppies (9–12) are hostile.

survey of guide dogs in America [59], although a similar survey in Australia reported high heritability in the evaluations of "success at becoming a guide dog" and "fear" (Table 1) [49]. Mackenzie et al [8] estimated the heritability for temperament scores of working German Shepherds as 0.51. High (desirable) scores were associated with poor hip conformation.

We could see more detail in some reviews about the general theory of classic genetic research, bringing together particulars that stretch across time and topic [15,18,63]. Although the results of classic Mendelian research on heredity have contributed greatly to breeding programs for working dogs, for example, it is not possible to apply them to programs that have to suit individual temperaments, such as the treatment of behavioral problems and training programs.

Feline temperament seems to be more easily and consistently described than canine temperament, perhaps because we demand less of cats. There have been four studies on the inheritance of temperament in cats. Adamec et al [10] tested laboratory-raised kittens with strange people and with the vocalization of an aggressive adult cat. By 10 weeks, the cats demonstrated behavior that would persist into adulthood; 25% of the cats were fearful. Cats' reactions to other people can be equable, hostile, fearful, or sociable. Turner et al [11] found that litters sired by one of two tom cats and out of several queens differed in sociability and hostility depending on which tom

Table 1
Heritability of various traits

Breed	Trait	Heritability
English Setter	Hunting eagerness	0.22
German Wire-Haired Pointer	Water retrieving	0.32
German Short-Haired Pointer	Tracking	0.48
German Shepherd Dog	Temperament	0.51
Labrador Retriever	Nervousness	0.58

Data from Houpt KA, Willis MB. Genetics of behaviour. In: Ruvinsky A, Sampson J, editors. The genetics of the dog. New York: CABI Publishing; 2001. p. 371–400.

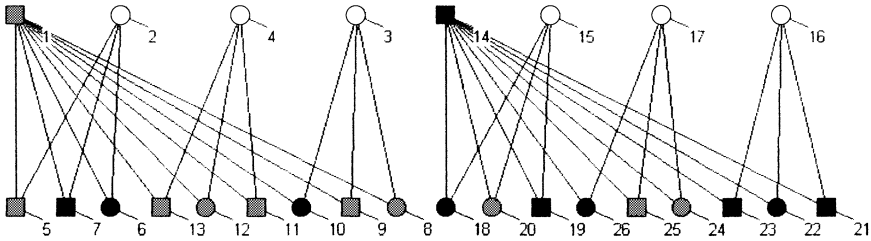

Fig. 2. Paternal effect. Black symbols indicate hostile behavior. Gray symbols indicate friendly behavior. White symbols indicate unknown temperament. Squares indicate males, and circles indicate females. When a friendly tom (1) is bred to several queens of unknown temperament (2–4), most of the kittens (5–13) are friendly. When a hostile tom (14) is bred to several queens (15–17) of unknown temperament, most of the kittens (18–26) are hostile.

sired them. This indicates a paternal effect (Fig. 2). A further study using the same two toms tested the effect of handling and paternity. The kittens were handled daily from 2 to 12 weeks of age. The tests were approach to a familiar person or a strange person and approach to a novel object, a box. The results were that handled kittens of friendly fathers were more likely to approach and interact with people and more likely to approach and enter the box. The unhandled kittens of the unfriendly father were least likely to approach people or the box. This indicates a general tendency to be either bold or fearful. Handling did not affect approach to the box, indicating that socialization is specific to people and not to all stimuli [12]. Reisner et al [13] also studied the effect of handling and paternity. Thirteen litters sired by five toms were tested. Kittens were weaned at 5 weeks and handled for 15 minutes three times a week for 3 weeks (ie, nine handling bouts). Temperament tests commenced at 8 weeks and were repeated four times. The temperament test consisted of a friendliness test and a response to restraint test. In the friendliness test, one of the handlers sat in a circle and the latency for the kitten to approach and tail posture were measured. The kitten's response to restraint for venepuncture was scored in the handling test. The results indicated no differences as a result of early handling but a significant litter effect. The offspring of two of the five toms were friendlier than those of the other three toms [13]. This study confirms the British finding of a paternal effect on kitten temperament. No doubt if the kittens of one tom and several queens were tested, an even stronger maternal effect would be found as was the case in dogs.

The complexities of the interaction between genetics and development are seen in the calico cat cloned through nuclear transplantation, which was born in 2002. The pattern of colored and white fur of the clone was different from the pattern of the donor cat [14]. Early in embryogenesis, all but one X chromosome are functionally inactivated through a process called X chromosome inactivation. The gene encoding orange coat color is X-linked (ie, on the X chromosome). Black color is encoded by either codominant

allele on the X chromosome. In black patches, the X chromosome bearing the orange allele has been inactivated and the X chromosome bearing the nonorange allele is active. In patches of orange fur, the X chromosome bearing the orange allele is activated. The random nature of X chromosome inactivation is evident—there are relatively large patches of both black and orange. If chance plays a part in simple pigmentation, it surely may be involved in emotional reactivity as well.

Genetic research concerning behavioral problems

Dogs have a long history as domestic animals. As a result of ongoing intensive breeding improvements for various purposes, such as hunting and working, there are now, if we limit ourselves to the main ones found around the world, more than 140 breeds. They vary in shape and size from the tiny Chihuahua to the enormous Great Dane. Just as in looks, their behavioral characteristics differ greatly according to breed; some dogs are brave, determined, and aggressive, whereas others are friendly and affectionate to everyone (Fig. 3). Despite this, scientific investigations into the relation between breed and temperament have been sparse. Hart and Hart [15] at the University of California surveyed obedience judges and veterinarians as to their opinions about 13 behavioral characteristics of 54 representative breeds. Unsurprisingly, breeds used as guard dogs like the Doberman Pinscher and German Shepherd ranked high in the behavioral traits of territorial defense and watchdog barking, whereas hunting dogs like the Labrador Retriever and Golden Retriever showed little aggressiveness and were highly responsive to obedience training. It was shown in this way that differences between breeds in terms of behavioral characteristics were quantifiable. The influence of hereditary factors was indicated for the traits of excitability and general activity.

The frequency of behavioral problems concerned with temperament, such as aggressive behavior, level of anxiety, and obsessive-compulsive disorder

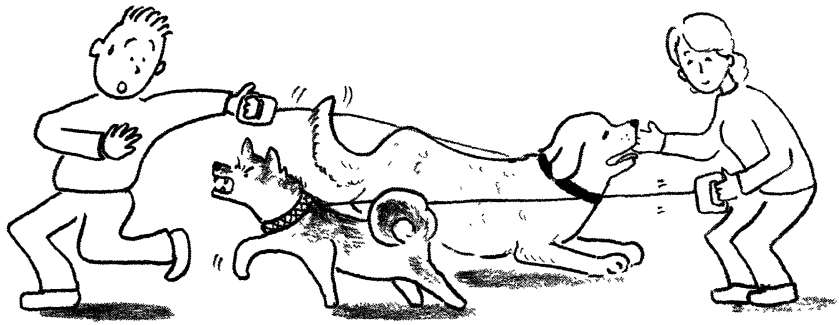

Fig. 3. Each breed has characteristic behavioral traits. Most Golden Retrievers are affectionate to people, whereas most Shibas show aggression toward strangers.

(stereotypy), varies according to breed, which suggests a connection with hereditary factors. When aggressiveness appeared in Bernese Mountain dogs, it was quickly eradicated, or at least reduced in frequency, by selective breeding, indicating a heritable cause of the misbehavior [16].

There are some interesting data concerning connections between coat color and aggressiveness. When queried, cat fanciers and veterinarians state that tortoiseshell or calico cats are quite aggressive. To investigate this, we compared the frequency with which cats of various coat colors—black, orange, and tricolor—are presented to the Cornell University Hospital for Animals for medical problems and to the Animal Behavior Clinic for behavioral problems. There was no significant difference in the proportions of coat colors. There was a significant effect, and that was that cats described by the owner as "and white" (ie, black and white, orange and white) were less likely to be presented for behavioral problems.

Podberscek et al [17] of Cambridge University conducted a survey among owners of English Cocker Spaniels concerning the aggressive behavior of their dogs. Dogs with a coat of a solid color rather than a particolored coat and dogs with red or golden coats rather than black coats tended to exhibit aggressive behavior. Houpt and Willis [18] at Cornell University analyzed data concerning the coat color of Labrador Retrievers. Their results showed that yellow Labrador Retrievers made up a larger proportion of dogs presented for aggressive behavior than those presented for medical problems, whereas aggressive chocolate and black Labrador Retrievers did not differ in proportion from that of the medical population. Because coat color is largely genetic, according to Mendelian laws, these data seem to point to the possibility that tendencies toward aggressive behavior may be hereditary and coinherited with genes controlling pigmentation. There is a direct metabolic reason why coat color might be linked to aggression. DOPA is the precursor of dopamine, a neurotransmitter, and of the pigment melanin DOPA. Genes that code for the enzyme that synthesizes DOPA and its products are probably involved in some way with the aggressive behavior associated with coat color. The relation between coat color and temperament is a topic that researchers must consider seriously in the future.

It is well known that there are differences between male and female dogs regarding the frequency of problem behavior. It has been reported that dominance-related aggression and territorial aggression are much more common in male dogs [47,51,52,54,61]. Separation anxiety is also suffered more by male dogs in some reports [53,57,60,62]. Such tendencies are unrelated to whether the animal has been castrated or spayed, which indicates that they are not the product of adult sexual hormone level. Hormones can affect an animal activationally by their presence at the moment in the blood stream or organizationally by their effect on the fetal brain during development. The lack of effect of castration on most types of aggression indicates that it may be the organizational effect of androgens that has lowered the threshold for aggression in intact and castrated male

dogs. In addition to the hormonal effects, some genes related to behavioral traits (eg, monoamine oxidase [20] and the serotonin 1c receptor [56]) are located on human sex chromosomes; such genes, if present on sex chromosomes of dogs, may well be connected to problem behavior.

One behavioral problem that does not occur frequently but may fail to be recognized is canine narcolepsy. This closely resembles human narcolepsy and cataplexy triggered by a positive emotion, and sudden episodes of muscle weakness akin to rapid eye movement (REM) sleep-associated atonia are produced. Narcolepsy in human beings is generally sporadic and obviously hereditary, whereas in dogs, it has been confirmed that it is autosomal recessive in transmission with full penetrance. In the 1980s, much research was carried out regarding genetic linkages by backcrossing such animals to discover the pathogenic gene. In 1999, Lin et al [27] at Stanford University reported that by using positional cloning, they had determined that canine narcolepsy originated from the regional deletion of hypocretin (orexin) receptor 2. Although at this point, we do not know if there is any causative relation between the mutation of this gene and human narcolepsy [25], the concentration of hypocretin in cerebrospinal fluid is low among human patients [28] and some narcoleptic dogs [9]. This kind of approach using dogs might provide valuable information applicable to the human clinical field. Narcolepsy seems to be a neurodegenerative disease in which there is atrophy of orexin cells.

There seem to be genetic differences in the frequency of some behavioral problems within breeds. The most obvious one is wool sucking. Several groups have noted that Siamese cats are most likely to be wool suckers [29,30]. In fact, they do not suck but rather chew with their molars as they would chew gristly prey. The cats seek out fabric and prefer loosely woven wool over woolen suiting material. The latency to chew wool is shortened by fasting, indicating a dietary basis. Furthermore, the medication clomipramine, which is most helpful in treating canine obsessive-compulsive problems like tail chasing and lick granulomas, is not effective in reducing the frequency of wool chewing. If one particular item is available to the cat, it is likely to eat a few holes in it and then to seek other material. This indicates that although wool is attractive, it is not meeting the needs of the cat; thus, the cat seeks something else. There is at least a component of roughage craving, because exposure to the outdoors during the growing season or access to a cat garden helps to reduce the frequency of wool chewing. Other suggested treatments are tough meat and raw chicken wings.

Recent research trends and directions

Temperament is related to the style of emotional cognition, which varies with the individual. When a dog reacts to stimuli (eg, meeting a person it does not know), the visual input is sent to the amygdala of the limbic system. This is the center for biologic value judgments and the source of emotional reactions.

Wary dogs (or those with a high level of anxiety) see people they do not know as a threat; thus, they bark or growl to make the person go away, but if this does not intimidate, they attempt to flee. At this point, the reaction to emergencies known as "fight or flight" comes into play; the heartbeat becomes rapid, the hackles rise, and the blood pressure rises. At the same time, the unpleasant emotions of fear and anger probably arise. Conversely, in the same situation, a friendly dog wags its tail happily and greets the person. The biologic value judgment mechanism in the brain tells the dog it should approach the person, and pleasant emotions may arise. Thus, the same stimulus may have different behavioral reactions depending on the state of the emotional cognition. This is temperament and is the basis of the individuality of each animal. There seems to be little difference among animals in the area of the brain that governs such emotional reactions, and there is a high degree of similarity between human beings and dogs.

In recent years, research into the genetic base of temperament in human beings has drawn a great deal of attention. Research related to the heredity of personality in monozygotic twins has shown that individual personalities are determined by hereditary and environmental factors fairly equally [31]. The earliest hereditary factor recognized as related to personality was genetic polymorphism related to the dopamine D4 receptor [32]. The dopamine receptor, which is linked to the emotions, is broadly divided into five subtypes from D1 through D5; there exists a repetitive element in the exon 3 domain of the D4 receptor, and this is known to affect the rate of transmission of information after the dopamine has bound to the receptor. People with a high repetitive rate tend to be highly novelty seeking. Extrapolating these results to an investigation of the same area in dogs, it has been demonstrated clearly that Shiba breed dogs, with a strong territorial instinct, have a longer repetitive element in the exon 3 domain than Golden Retrievers (see Fig. 3) [33]. It has also been reported in human beings that serotonin-related genes are related to levels of anxiety, aggression, and harm avoidance [1,22,58]. Because dopamine and serotonin are so intimately involved in changes in mood and the emotions, these neurotransmitters have been considered as targets of various antianxiety drugs, antidepressant drugs, and stimulants [23,34].

Such research began within the human psychiatry field, but because the influence of social, cultural, and environmental factors is so great on the development of brain functions in human beings and on the development of the personality, it is not easy to determine causal relations, and this has been an obstacle to further research. In contrast, when we try to analyze laboratory mice and rats whose environment can be easily controlled, it is difficult to make a detailed personality analysis based on behavioral parameters, because there seem to be few individual differences in personality traits. Companion animals like cats and dogs, which have a simpler system than human beings but whose rich individuality can be described, would seem to be ideal as objects for this kind of research. In

our laboratory, we have begun to analyze the various kinds of genetic polymorphisms related to neurotransmitters, centering on dogs.

Single nucleotide polymorphisms (SNPs) are a class of DNA polymorphisms that have proven useful as markers in mapping genes. An example would be a series of the 3000 base pairs in which a single base pair can differ between individuals. If a gene that modified behavior in a fearful dog is always inherited along with a particular marker, the gene and the SNP marker are linked. The position on the chromosome of the gene for fearfulness can be identified. We have already confirmed several SNPs accompanying amino acid substitution in the exon domain of some genes [unpublished data]. Because the brain function that governs emotion is preserved across a wide range of animals, it may be inferred that it is possible to apply our research results to other animals. We hope that the discovery of genes related to temperament is useful in improving the human–companion animal bond by elimination of traits leading to dominance, aggression, and separation anxiety and by selective breeding for desirable characteristics. Knowledge of a dog's genotype could lead to screening programs suited to the individual (Table 2).

Research into genes governing behavior has only just begun, but, already, there are more than 30 genes that are postulated to be related to temperament, and this number continues to rise (Table 3). Four types of genetic polymorphisms are so far known to be related to individuality in human beings: restriction fragment length polymorphism (RFLP, one type of SNP) [19], variable number of tandem repeat (VNTR) [6,35], microsatellite (2–4 tandem repeats) [36], and SNP [7]. Because the microsatellite is a thousand times more susceptible to mutation across generations than the SNP, it is not considered suitable as a marker for genes related to temperament. It is probably not possible to explain animal temperament in terms of a single gene, as reports on numerous such genes indicate. Rather, small variations in the coding of multiple genes may constitute temperament differences. The structure of the human genome has been made public by the Human Genome Project [21,37], and genetic research is now moving toward the postgenome age. Recently developed microarray technology is able to analyze the expression pattern of a large number of genes at the same time from a small sample and can also distinguish the SNP [38,39]. Employing such technology, we may in the near future be able to confirm genetic characteristics of a companion animal from its genes originating in blood (white blood cell), saliva (cheek swab), or coat hair (radix pili) (Table 3, Fig. 4).

We also know that the father's genes influence the daughter's future maternal behavior [40,41]. The Peg1 (Mest) and Peg3 genes, which have been called the imprinting genes, are the monoallelic genes originating in the father, and the daughter of a mutant mouse father in which these genes were not expressed was not able to exhibit sufficient maternal behavior when she became a mother. Because this daughter had few oxytocin cells in

the paraventricular nucleus of the hypothalamus, the father's mutation obviously influenced the oxytocin neurons in the daughter (Fig. 5).

Nature or nurture?

Even though hereditary factors are important as the base on which personality is formed, it is impossible to ignore the importance of environmental influence during the period after birth. Because the

Table 2
Definitions

Gene	The fundamental unit of heredity composed of sequences of hundreds to thousands of nucleotide bases strung together in giant DNA molecules, the chromosomes. Genes have two functional units: the coding region, which is transcribed into RNA and then translated into protein based on the three-base genetic code, and the promoter regions, which flank the coding region and determine the timing, amount, and anatomic localization of gene expression and protein synthesis. In eukaryotic cells, the RNA transcribed from the DNA sequence of a gene's coding region can be "cut and pasted" during RNA splicing to produce variations in protein translated from the underlying genetic code. Exons are the portion of the gene that is included in the final mRNA transcript of a gene and thus are translated into part of a protein. Introns are the segments of a gene located between the exons that are transcribed into RNA but are cut out from the mRNA and degraded with the nucleus, such that they are never translated into protein. The function of this "junk DNA" is unknown, although it may contribute to gene regulation.
Single nucleotide polymorphism (SNP)	A single necleotide within the DNA sequence of hundreds or thousands of bases that make up a gene may or may not have an effect on the protein coded for by that gene, but the presence of a distinct SNP can be used as a marker regardless of functional consequences.
Tandem repeats	Tandem repeat regions of the gene are particularly susceptible to replication mutations, in which the gene is extended in length through the inadvertent replication of a short subsequence, or unit, of nucleotides, during meiosis. Two forms of tandem repeats are commonly analyzed: variable length tandem repeats (VLTRs) consist of multiple repeats of DNA units from 9 to 80 base pairs, and microsatellites are tandem repeats of units of one to six base pairs. Because the specific number of repeats at any VTLR or microsatellite site in the genome may vary between individuals of subpopulations, the size of specific VTLRs or microsatellites may serve as a genetic marker.

Table 2 (*continued*)

Microsatellites	Short tandem repeat sequences of two to six base pairs
Restriction length fragment polymorphism (RFLP)	DNA is digested with a restriction enzyme (an enzyme that cleaves DNA at specific sites) into shorter fragments of DNA. If there is variation in the DNA sequence between the cleavage sites, the pattern of fragment lengths differs between individuals or subpopulations. These patterns can thus be used to distinguish between the individuals.
Microarrays	Specific tandem repeats of SNPs can be detected one at a time by amplifying DNA using polymerase chain reaction. To detect multiple polymorphisms at the same time, small quantities of known DNA sequences (corresponding to polymorphisms of interest) can be arrayed as small spots on a microscope slide. Thousands of different polymorphisms can be spotted in a single microarray. DNA to be analyzed from an individual can be incubated on the microarray; the presence of a specific polymorphism in the individual is detected when the DNA sticks to the corresponding spot on the array. Because polymorphisms within different genes and chromosomes stick to the array in parallel and are revealed simultaneously, microarrays promise high throughput characterization and screening of patient DNA.

impossibility of deciding whether nature or nurture is the deciding factor has been shown by discussion over many years, both are indispensable in the formation of personality [42].

From developmental and behavioral research conducted down to the present, it can be predicted that socialization is closely related to the development of the central nervous system, particularly the hypothalamus and the limbic system, which govern emotional response. The period of socialization, which is determined for each species, is when the dog or cat is able, without any anxiety or fear, to regard other dogs or cats as well as other animals, including human beings, as being on his list of acquaintances.

Because cats and dogs are born with immature eyes and ears, their socialization period cannot begin until they are able to perceive the environment. The canine socialization period lasts from around 3 to 12 weeks [48]. The feline socialization period is 2 to 5 weeks [24]. A new understanding of the influence of the early environment has been gained through experiments on rodents. Characteristic maternal behavior of small rodents, such as mice and rats, comprises lactation, grooming, stimulation for elimination, and retrieving. It is clear that there is, in particular, a close connection between grooming in the early stage and later behavioral patterns. On the one hand, young rats that have received a lot of grooming from the mother tend to be contented individuals when grown; conversely, young rats that do not receive much grooming display an aggressive character and a high level of anxiety later (Fig. 6) [43]. Further, maternal grooming also influences the development

Table 3
Polymorphic genes positively related to temperament or psychic disease (reports are collected from MEDLINE database from 1966 to 2000)

Target gene and temperament	References
5-HT transporter	
Anxiety (VNTR)	Science 274:1527–31, J Hum Genet 44:15–7
Harm avoidance (VNTR)	Psychiatr Genet 8:41–4, Arch Gen Psychiatry 55:936–40
Novelty seeking (VNTR)	Biol Psychiatry 43:908–12
Depression (VNTR)	Am J Med Genet 81:58–63, Psychol Med 29:1249–54
	Prog Neuropsychopharmacol Biol Psychiatry 23:55–65
Alcoholism (VNTR)	Biol Psychiatry 43:908–12, Biol Psychiatry 45:647–51
Smoking (VNTR)	Cancer Epidemiol 8:831–3
5-HT1B receptor	
Antisocial alcoholism (SNP)	Arch Gen Psychiatry 55:989–94
Antisocial alcoholism (VNTR)	Arch Gen Psychiatry 55:989–94
5-HT2A receptor	
Schizophrenia (SNP)	Lancet 9011:1294–6, J Psychiatr Neurosci 24:141–6
Clozapine response (SNP)	Lancet 8970:281–2, Schizophr Res 32:93–9
Clozapine response in schizophrenia (SNPa)	Neurosci Lett 217:177–8, Neuropsychopharmacology 19:123–32
Seasonal affective disorder (SNP)	Mol Psychiatry 4:89–92, J Affect Disord 53:203–10
Anorexia nervosa (SNP)	Neurosci Lett 277:134–6
Bulimia nervosa (SNP)	Neurosci Lett 277:134–6
5-HT2C receptor	
Clozapine response (SNPa)	Neuroreport 7:169–72
Bipolar disorder (SNPa)	Neurosci Lett 212:65–7
Reward dependence (SNPa)	Am J Med Genet 74:65–2
5-HT6 receptor	
Clozapine response in schizophrenia (SNP)	Neuroreport 10:1231–3
Alzheimer's disease (SNP)	Neurosci Lett 276:138–9
5-HT7 receptor	
Alcoholism impulsivity (SNPa)	Psychiatr Res 77:139–45
Dopamine transporter	
Attention-deficit hyperactivity (VNTR)	Am J Med Genet 56:993–8, Mol Psychiatry 2:311–3, Genomics 52:289–97
Bipolar disorder (VNTR)	Am J Med Genet 67:533–40
Novelty seeking (VNTR)	Biol Psychiatry 42:1070–2, Health Psychol 18:7–13
Schizophrenia (VNTR)	Eur Neurol 38(Suppl 1):6–10
Alcoholism (VNTR, SNP)	Psychiatr Genet 7:87–91, Mol Psychiatry 4:552–7
Smoking (VNTR)	Health Psychol 18:7–13
Dopamine D2 receptor	
Alcoholism (RFLP)	Psychiatr Genet 7:87–91, Biol Psychiatry 43:40–51
Novelty seeking (RFLP)	Am J Med Genet 81:257–67
Reward dependence (RFLP)	Am J Med Genet 81:257–67
Harm avoidance (RFLP)	Am J Med Genet 81:257–67
Schizophrenia (RFLP, SNP)	Mol Psychiatry 2:239–46, Schizophr Res 40:31–6
Dopamine D3 receptor	
Schizophrenia (RFLP)	J Med Genet 29:858–60, Am J Med Genet 67:63–70, Genomics 52:289–97
Bipolar disorder (RFLP)	Genomics 52:289–97
Novelty seeking (RFLP)	Am J Med Genet 81:192–4, Psychiatr Genet 9:17–21

Table 3 (*continued*)

Target gene and temperament	References
Dopamine D4 receptor	
Novelty seeking (VNTR)	Nat Genet 12:78–80, Am J Med Genet 74:501–3, Am J Med Genet 81:257–67
Schizophrenia (VNTR)	Eur Neurol 38(Suppl 1):6–10
Attention-deficit hyperactivity (VNTR)	Mol Psychiatry 3:38–41, Mol Psychiatry 3:419–26, Mol Psychiatry 3:427–30, Am J Psychiatry 156:768–70
Bipolar disorder (VNTR)	Am J Med Genet 88:486–91
Harm avoidance (VNTR)	Am J Med Genet 88:634–41
Dopamine D5 receptor	
Autism (SNPa)	Am J Med Genet 81:172–8
GABA-A alpha 6 receptor	
Alcoholism (SNPa)	Biol Psychiatry 45:647–51
Cholecystokinin receptor	
Alcoholism (SNP)	Alcohol Clin Exp Res 22(Suppl 3):93S–6
Catechol-o-methyltransferase (COMT)	
Schizophrenia (SNPa)	Psychiatr Genet 6:131–3, Psychiatr Res 69:71–7, Neurosci Lett 243:109–12
Parkinson's disease (SNPa)	Neurosci Lett 221:202–4, J Neural Transm 104:1313–7
Obsessive-compulsive disorder (SNPa)	Proc Natl Acad Sci USA 94:4572–5, Psychiatr Genet 7:97–101
Bipolar disorder (SNPa)	Psychiatr Genet 7:97–101, Pharmacogenetics 7:349–53, Mol Psychiatry 3:342–5, Mol Psychiatry 3:346–9
Attention-deficit hyperactivity (SNPa)	Am J Med Genet 88:497–502
Dopamine beta-hydroxylase	
Drug-treated schizophrenia (microsatellite)	Biol Psychiatry 41:762–7
Schizophrenia (RFLP)	Schizophr Res 22:77–80
Monoamine oxidase A	
Impulsive aggression (SNP)	Science 5133:578–80
Bipolar disorder (microsatellite)	Am J Hum Genet 54:1122–4
Panic disorder (VNTR)	Hum Mol Genet 8:621–4
Antisocial alcoholism (VNTR, RFLP)	Psychiatr Res 86:67–72, Genomics 55:290–5
Monoamine oxydase B	
Parkinson's disease (microsatellite, SNP)	Mov Disord 14:219–24, Am J Med Genet 74:154–6
Tryptophan hydroxylase	
Impulsive aggression (SNP)	Am J Med Genet 81:13–7
Bipolar disorder (SNP)	Arch Gen Psychiatry 55:33–7
Suicidal behavior, impulsivity (SNP)	Genomics 52:289–97, Arch Gen Psychiatry 55:593–602
Aggression, anger-related traits (SNP)	Biol Psychiatry 45:603–14
Tyrosine hydroxylase	
Bipolar disorder (RFLP)	Am J Med Genet 74:289–95, Am J Med Genet 81:127–30
Schizophrenia (VNTR)	Eur Arch Psychiatr Clin Neurosci 248:61–3
Deliberation, dutifulness (VNTR)	Psychiatr Res 95:1–8

Polymorphic types are shown in parentheses.

Abbreviations: GABA, gamma aminobutyric acid; RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism; SNPa, SNP accompanying amino acid substitution; VNTR, variable number of tandem repeats; microsatellite, two to four tandem repeats.

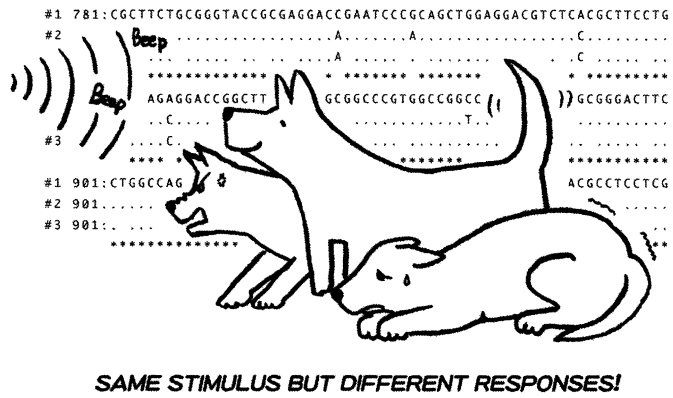

Fig. 4. Development of molecular biology may allow us to solve the mystery of individuality based on genomic polymorphism.

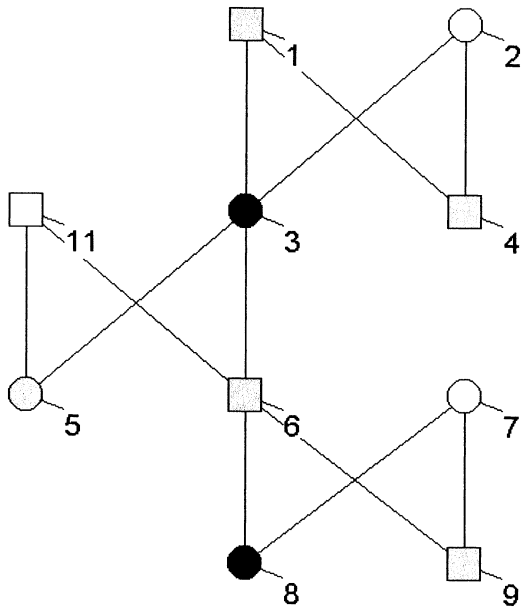

Fig. 5. Paternal imprinting. A mutation for poor maternal behavior is expressed (activated) only when inherited from the father (1). The daughter (3) of a male carrying the mutation (1) has poor maternal behavior, but her daughter (5) has normal maternal behavior even though she is a carrier. Her son (6) carries the mutation; his daughter (8) will have poor maternal behavior, and her son (9) will be a carrier. Black symbols indicate poor maternal behavior. Gray symbols indicate carriers. White symbols are normal. Squares indicate males, and circles indicate females.

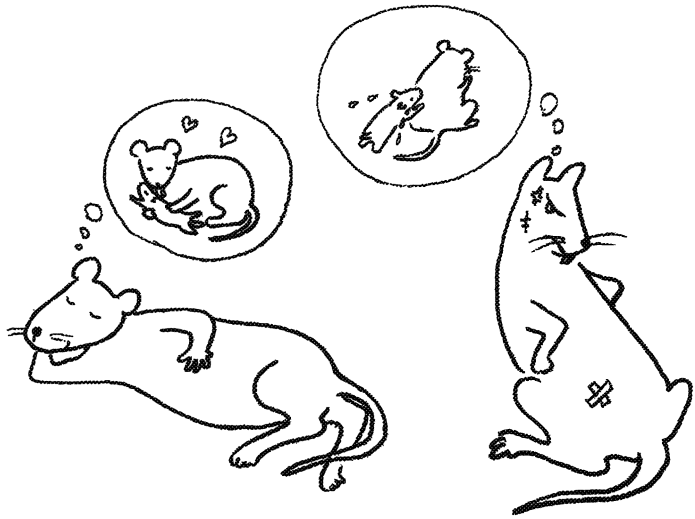

Fig. 6. The level of maternal care affects the later behavioral pattern of the grown rat. Young rats that have received a lot of grooming from the mother tend to be contented individuals, whereas young rats that have not received much grooming display an aggressive character and a high level of anxiety.

of learning abilities in young rats [26]. Experiments with foster mothers have shown that these tendencies are not hereditary [44]. These results indicate clearly that the degree of care the mother gives its young determines the later behavioral pattern of the grown rat. Studies of the mechanism by which young rats show high levels of anxiety focus on the role of the corticotropin-releasing factor (CRF), a neuropeptide that governs the endocrine system (ie, the hypothalamus-pituitary-adrenal cortex axis) [45]. Investigations of individuals that did not receive much grooming as babies from their mothers show an increase of CRF mRNA in the paraventricular nucleus of the hypothalamus and an increase of the CRF receptor in the amygdala. By contrast, individuals that have received a lot of grooming exhibit an increase in the hippocampus of the glucocorticoid receptor, giving negative feedback to the CRF such that the CRF is easily controlled. This shows that early environment is an important influence on behavioral patterns and that the care a mother gives her young, whether good or bad, brings permanent change to the neural mechanism of the brain. This mechanism also holds true for pigs to some extent [46], and it may be possible to extrapolate this to companion animals like cats and dogs as well.

It is said that when a certain breed becomes popular, behavioral problems arise after some time. One factor is hereditary in that unsuitable breeding has occurred in the interests of consumerism. We must also consider the possibility that the animals, being popular consumer items, are removed from their mother and siblings at too early an age and are injured psychologically by being placed alone in the window of a pet shop or by

being transported over a long distance during the important time when the basis of emotions is being formed [50].

Summary

The influence of hereditary and environmental factors is indispensable as the foundation on which the temperament of an animal is formed. Genetic research on animal temperament has experienced a turning point in recent years as a result of the development of molecular biology. In the near future, it may be possible to explain the formation process of animal temperament as the two fields share their research. We look forward to applying these research results to the development of new genetic treatment methods for problem behavior and training programs suited to the individual.

Acknowledgment

The authors thank Prof Yuji Mori (Veterinary Ethology, The University of Tokyo) for his valuable comments and generous permission to use his drawings, T.A. Houpt for Table 2, and E.J. Pollock for Figs. 1, 2, and 5.

References

[1] Lesch KP, Merschdorf U. Impulsivity, aggression, and serotonin: a molecular psychobiological perspective. Behav Sci Law 2000;18:581–604.
[2] Thorne FC. The inheritance of shyness in dogs. J Genet Psychol 1944;65:275–9.
[3] Dykman RA, Murphree OD, Peters JE. Like begets like: behavioral tests, classical autonomic and motor conditioning, and operant conditioning in two strains of pointer dogs. Ann NY Acad Sci 1969;159:976–1007.
[4] Scott JP, Fuller JL. Genetics and the social behavior of the dog. The classic study. Chicago: The University of Chicago Press; 1965.
[5] Freedman DG. Constitutional and environmental interactions in rearing of four breeds of dogs. Science 1958;127:585–6.
[6] Nakamura Y, Koyama K, Matsushima M. VNTR (variable number of tandem repeat) sequences as transcriptional, translational, or functional regulators. J Hum Genet 1998;43: 149–152.
[7] Comings DE, Johnson JP, Gonzalez NS, et al. Association between the adrenergic alpha 2A receptor gene (ADRA2A) and measures of irritability, hostility, impulsivity and memory in normal subjects. Psychiatr Genet 2000;10:39–42.
[8] Mackenzie SA, Oltenacu EAB, Leighton E. Heritability estimate for temperament scores in German Shepherd Dogs and its genetic correlation with hip dysplasia. Behav Gen 1985; 15:475–82.
[9] Ripley B, Fujiki N, Okura M, et al. Hypocretin levels in sporadic and familial cases of canine narcolepsy. Neurobiol Dis 2001;8:525–34.
[10] Adamec RE, Stark-Adamec C, Livingston KE. The expression of an early developmentally emergent defensive bias in the adult domestic cat (*Felis catus*) in non-predatory situations. Appl Anim Ethol 1983;10:89–108.
[11] Turner DC, Feaver J, Mendl M, Bateson P. Variation in domestic cat behaviour towards humans: a paternal effect. Anim Behav 1986;34:1890–2.

[12] McCune S. The impact of paternity and early socialisation on the development of cats' behaviour to people and novel objects. Appl Anim Behav Sci 1995;45:109–24.
[13] Reisner IR, Houpt KA, Quimby KW. Friendliness to humans and defensive aggression in cats: the influence of handling and paternity. Physiol Behav 1994;55:1119–24.
[14] Shin T, Kraemer D, Pryor J, et al. A cat cloned by nuclear transplantation. Nature 2002;415:859.
[15] Hart BL, Hart LA. The perfect puppy. New York: WH Freeman and Company; 1988.
[16] Van Der Velden NA, De Weerdt CJ, Brooymans-Schallenberg JHC, et al. An abnormal behavioural trait in Bernese Mountain Dogs (Berner sennenhund). Tijdschr Diergeneesk 1976;101:403–7.
[17] Podberscek AL, Serpell J. The English Cocker Spaniel: preliminary findings on aggressive behaviour. Appl Anim Behav Sci 1996;47:75–89.
[18] Houpt KA, Willis MB. Genetics of behaviour. In: Ruvinsky A, Sampson J, editors. The genetics of the dog. New York: CABI Publishing; 2001. 371–400.
[19] Blum K, Noble EP, Sheridan PJ, et al. Genetic predisposition in alcoholism: association of the D2 dopamine receptor TaqI B1 RFLP with severe alcoholics. Alcohol 1993;10: 59–67.
[20] Grimsby J, Chen K, Wang LJ, et al. Human monoamine oxidase A and B genes exhibit identical exon-intron organization. Proc Natl Acad Sci USA 1991;88:3637–41.
[21] Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. Nature 2001;409:860–921.
[22] Lesch KP, Bengel D, Heils A, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 1996;274:1527–31.
[23] Petty F, Davis LL, Kabel D, et al. Serotonin dysfunction disorders: a behavioral neurochemistry perspective. J Clin Psychiatry 1996;57:11–6.
[24] Martin P, Bateson P. Behavioural development in the cat. In: Turner DC, Bateson P, editors. The domestic cat. The biology of its behaviour. Cambridge: University of Cambridge Press; 1988, p. 9–22.
[25] Olafsdottir BR, Rye DB, Scammell TE, et al. Polymorphisms in hypocretin/orexin pathway genes and narcolepsy. Neurology 2001;57:1896–9.
[26] Liu D, Diorio J, Day JC, et al. Maternal care, hippocampal synaptogenesis and cognitive development in rats. Nat Neurosci 2000;3:799–806.
[27] Lin L, Faraco J, Li R, et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 1999;98:365–76.
[28] Nishino S, Ripley B, Overeem S, et al. Low cerebrospinal fluid hypocretin (orexin) and altered energy homeostasis in human narcolepsy. Ann Neurol 2001;50:381–8.
[29] Bradshaw JWS. The behaviour of the domestic cat. Wallingford, UK: CAB International; 1992.
[30] Houpt KA. Feeding and drinking behavior problems. Vet Clin North Am Small Anim Pract 1991;21:281–98.
[31] Plomin R. The role of inheritance in behavior. Science 1990;248:183–8.
[32] Benjamin J, Li L, Patterson C, et al. Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. Nat Genet 1996;12:1–84.
[33] Niimi Y, Inoue-Murayama M, Murayama Y, et al. Allelic variation of the D4 dopamine receptor polymorphic region in two dog breeds, Golden Retriever and Shiba. Veterinary Medicine 1999;61:1281–6.
[34] Comings DE, Blum K. Reward deficiency syndrome: genetic aspects of behavioral disorders. Prog Brain Res 2000;126:325–41.
[35] Manuck SB, Flory JD, Ferrell RE, et al. A regulatory polymorphism of the monoamine oxidase-A gene may be associated with variability in aggression, impulsivity, and central nervous system serotonergic responsivity. Psychiatry Res 2000;95:9–23.
[36] Jonsson EG, von Gertten C, Gustavsson JP, et al. Androgen receptor trinucleotide repeat polymorphism and personality traits. Psychiatr Genet 2001;11:19–23.

[37] Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. Science 2001;291:1304–51.
[38] Blohm DH, Guiseppi-Elie A. New developments in microarray technology. Curr Opin Biotechnol 2001;12:41–7.
[39] Tillib SV, Mirzabekov AD. Advances in the analysis of DNA sequence variations using oligonucleotide microchip technology. Curr Opin Biotechnol 2001;12:53–8.
[40] Lefebvre L, Viville S, Barton SC, et al. Abnormal maternal behaviour and growth retardation associated with loss of the imprinted gene Mest. Nat Genet 1998;20:163–9.
[41] Li L, Keverne EB, Aparicio SA, et al. Regulation of maternal behavior and offspring growth by paternally expressed Peg3. Science 1999;284:330–3.
[42] Meaney MJ. Nature, nurture, and the disunity of knowledge. Ann NY Acad Sci 2001; 935:50–61.
[43] Caldji C, Tannenbaum B, Sharma S, et al. Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. Proc Natl Acad Sci USA 1998;95:5335–40.
[44] Francis D, Diorio J, Liu D, et al. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. Science 1999;286:1155–8.
[45] Liu D, Diorio J, Tannenbaum B, et al. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. Science 1997;277:1659–62.
[46] Weaver SA, Aherne FX, Meaney MJ, et al. Neonatal handling permanently alters hypothalamic-pituitary- adrenal axis function, behaviour, and body weight in boars. J Endocrinol 2000;164:349–59.
[47] Borchelt PL. Aggressive behavior of dogs kept as companion animals: classification and influence of sex, reproductive status and breed. Appl Anim Ethol 1983;10:45–61.
[48] Freedman DG, King JA, Elliot E. Critical period in the social development of dogs. Science 1961;133:1016–7.
[49] Goddard ME, Beilharz RG. Genetic and environmental factors affecting the suitability of dogs as guide dogs for the blind. Theor Appl Genet 1982;62:97–102.
[50] Jagoe A, Serpel J. Owner characteristics and interactions and the prevalence of canine behavior problems. Appl Anim Behav Sci 1996;47:31–42.
[51] Landsberg GM. The distribution of canine behaviour cases at three behaviour referral practices. Veterinary Medicine 1991;86:1011–8.
[52] Line S, Voith VL. Dominance aggression of dogs towards people: behavior profile and response to treatment. Appl Anim Behav Sci 1986;16:77–83.
[53] Lund JD, Jorgensen MC. Separation anxiety in pet dogs behaviour patterns and time course of activity. In: Proceedings of the First Conference on Veterinary Behavioral Medicine. Potters Bar, UK: Universities Federation for Animal Welfare; 1997. p. 133–42.
[54] Lund JD, Agger JF, Vestergaard KS. Reported behaviour problems in pet dogs in Denmark: age distribution and influence of breed and gender. Prev Vet Med 1996;28:33–48.
[55] Mackenzie SA, Oltenacu EAB, Houpt KA. Canine behavioral genetics—a review. Appl Anim Behav Sci 1986;15:365–93.
[56] Milatovich A, Hsieh CL, Bonaminio G, et al. Serotonin receptor 1c gene assigned to X chromosome in human (band q24) and mouse (bands D-F4). Hum Mol Genet 1992;1: 681–684.
[57] Podberscek AL, Hsu Y, Serpell JA. Evaluation of clomipramine as an adjunct to behavioural therapy in the treatment of separation-related problems in dogs. Vet Rec 1999;145:365–9.
[58] Ricketts MH, Hamer RM, Sage JI, et al. Association of a serotonin transporter gene promoter polymorphism with harm avoidance behaviour in an elderly population. Psychiatr Genet 1998;8:41–4.
[59] Scott JP, Bielfelt SW. Analysis of the puppy testing program. In: Pfaffenberger CJ, Scott JP, Fuller JL, Ginsburg BE, Bielfelt SW, editors. Guide dogs for the blind: their selection, development and training. New York: Elsevier; 1976. p. 39–75.

[60] Takeuchi Y, Houpt KA, Scarlett JM. Evaluation of treatments for separation anxiety in dogs. JAVMA 2000;217:342–5.
[61] Takeuchi Y, Ogata N, Houpt KA, et al. Differences in background and outcome of three behavior problems of dogs. Appl Anim Behav Sci 2001;70:297–308.
[62] Voith VL, Borchelt PL. Separation anxiety in dogs. Compend Contin Educ Pract Vet 1985;7:42–52.
[63] Willis MB. Genetic aspects of dog behaviour with particular reference to working ability. In: Serpell J, editor. The domestic dog. Its evolution, behaviour, and interactions with people. New York: Cambridge University Press; 1995. p. 51–64.
[64] Wilsson E. The social interaction between mother and offspring during weaning in German Shepherd Dogs: individual differences between mothers and their effects on offspring. Appl Anim Behav Sci 1984/1985;13:101–12.