Review
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Health and temperaments of cloned working dogs

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Dogs serve human society in various ways by working at tasks that are based on their superior olfactory sensitivity. However, it has been reported that only about half of all trained dogs may qualify as working dogs through conventional breeding management because proper temperament and health are needed in addition to their innate scent detection ability. To overcome this low efficiency of breeding qualified working dogs, and to reduce the enormous costs of maintaining unqualified dogs, somatic cell nuclear transfer has been applied in the propagation of working dogs. Herein, we review the history of cloning working dogs and evaluate the health development, temperaments, and behavioral similarities among the cloned dogs. We also discuss concerns about dog cloning including those related to birth defects, lifespan, and cloning efficiency.

Keywords: behavior, cloning, health, working dog

Introduction

Dogs (*Canis familiaris*) have an essential role in human society that is based on utilizing their extraordinary scent detection ability to find drugs (drug detection dogs), illegal agricultural products (quarantine dogs), injured persons (rescue dogs), suspects (police dogs), etc. They can detect certain compounds with up to 100,000-fold higher sensitivity than humans due to their superior olfactory sensitivity [55,56] and their high number of olfactory neuroepithelial cells [22]. However, despite their innate scent detection ability, only a limited proportion of trained dogs are suitable for these types of work because suitable temperament and health qualities are needed to perform trained tasks in uncontrolled and/or unexpected environments [44]. Dog breeding management programs have been developed to maintain specific traits through the use of artificial selection, but only about half of conventionally bred, trained dogs may qualify as working dogs. For example, among 200 German Shepherd dogs within the Swedish Armed Forces, only 52% were found to have suitable temperaments [14]. Within Guide Dogs for the Blind Inc., Australia, 42.6% (313/735) of puppies were successfully trained as working dogs [44], whereas in The Seeing Eye guide dog school in the USA, 56% of 2,033 dogs graduated as qualified guide dogs [13]. The approximately 50% success rate in achieving a qualified working dog is related to efforts to improve temperament and health issues of dogs over several decades through the use of conventional breeding management programs. There are inherent problems associated with the remaining half of the dogs that fail to qualify; in particular, problems related to cost, time, labor, and financial resources. Moreover, if the unqualified dogs also fail to have applicants wishing to adopt them, such problems could last for more than a decade.

Somatic cell nuclear transfer (SCNT) is a technique used to produce an animal that has the same genetic information as the cell donor. In 2005, the first cloning of a dog via SCNT was achieved with the birth of Snuppy [36]. Lee *et al*. [36] established fibroblasts from ear skin tissue obtained from a 3-year-old male Afghan Hound and induced the donor cells to become quiescent by using contact inhibition. A quiescent, diploid donor cell was then injected into an enucleated metaphase II oocyte retrieved from a donor, and the cell-oocyte couplet was fused electrically. Artificial activation of the reconstructed embryos was induced, and, immediately after activation, the embryos were transferred into oviducts of recipient dogs. Consequently, the resulting cloned puppy had the same nuclear and mitochondrial genetic information as the

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cell donor and oocyte donor, respectively [8,29,37,42]. Since that first cloned dog, a variety of cloned dogs have been produced, and it has been reported that dog cloning using the SCNT technique can be successfully performed regardless of the sex (male [36] and female [25]), age (fetus [18], young adult [36], and old [24]), or breed (Afghan hound [25,36], miniature poodle [24], beagle [18,29], Labrador Retriever [35,43], Pekingese [46], German Shepherd [30,42], Sapsaree [23], and Gyeongju Donggyeong dog [8]) of the cell donor.

To overcome the low efficiency associated with producing qualified working dogs and the enormous maintenance costs associated with unqualified dogs obtained through traditional breeding management programs, a hypothesis was raised that cloning a working dog possessing good temperament and health could produce a puppy that would become a qualified dog. Up to January 2018, all of the dog cloning studies that have been reported have been conducted in South Korea. In this review, we have focused on studies into the cloning of working dogs in South Korea.

Table 1. Cloned working dogs reported previously

Cell donor			No. of clones	Reference
Affiliation	Breed	Age (yr)		
Customs Border Control Training Institute	Labrador Retriever	7	7	[43]
Korean National Police Agency	German Shepherd	8	2	[30]
Animal and Plant Quarantine Agency	Beagle	10	1	[29]
St. Sugar Cancer Sniffing Dog Training Center in Japan	Labrador Retriever	7	4	[35]
National 119 Rescue Headquarters	German Shepherd	10	2	[42]

History of Working Dog Cloning

A drug detection dog with an elite ability to find illegal drugs during customs searches, enrolled in the Korea Customs Service, was selected for use in the first attempt to clone a working dog. A skin biopsy was performed on the earflap of the dog, a 7-year-old male Labrador Retriever, by using an approach that required minimal restraint and invasiveness. Similar to the earlier study with Snuppy, fibroblast cultures were established from the skin tissue, and the production of seven cloned Labrador Retriever dogs was reported in 2009 by Oh *et al*. [43]. Except for one dog that had a leg fracture from an accident, all of the remaining six clones (100%) were able to pass the detector dog selection test with high scores [7]. This result was superior to that obtained with control dogs, born using a standard breeding management program, in which only one of four pups (25%) passed the selection test; moreover, they passed with a low score [7]. The Korea Customs Service announced that the successful application of cloning for the production of drug detection dogs could reduce their budget expenditures.

Based on those milestone results from our drug detection dog cloning project, in 2011, the Korean Rural Development Administration made an agreement with the Ministry of Agriculture, Food and Rural Affairs (Animal and Plant Quarantine Agency), the Ministry of National Defense (Army and Air Force), the Korea Customs Service (Customs Border Control Training Institute), the Korean National Police Agency, and the Ministry of Public Safety and Security (National 119 Rescue Headquarters) regarding the efficient management of national working dogs. The Rural Development Administration established a national cell bank for use in producing working dogs via SCNT, and it has provided cloned dogs derived from the cell bank to other institutes (Table 1).

In addition to research into the cloning of national working dogs, the production of a cloned cancer-sniffing dog was reported in 2015 [35]. Dogs can smell volatile organic compounds linked to cancer, such as alkanes, methylated alkanes, aromatic compounds, and benzene derivatives [12,39]. From the first suggestion of Williams and Pembroke [57] in 1989 that a dog's scent detection ability could be used in the diagnosis of cancers, this proposition has been confirmed in the detection of various cancers including bladder [58], lung [40], prostate [10], ovarian [19], and colorectal [52] cancers. A cancer-sniffing dog in the St. Sugar Cancer Sniffing Dog Training Center (Chiba, Japan) was reported to be able to detect colorectal cancer with high sensitivity (91%) and specificity (99%) in the exhaled breath and stool of patients [52]. Ear skin tissue derived from the cancer-sniffing dog in Japan was transferred to South Korea in phosphate-buffered saline supplemented with 1% (v/v) penicillin-streptomycin. Four cloned puppies were produced, but, unfortunately, only one could be assessed for its cancer detection ability due to ownership problems. After training, that dog was able to detect breast cancer from exhaled breath with similar sensitivity (93.9%) and specificity (99.5%) to those of its cell donor [52].

Healthy Development of Cloned Dogs

There have been concerns about the health of cloned animals ever since the beginning of mammalian cloning, with the development of Dolly the sheep [59]. Considering that approximately half of the trained dogs fail to be suitable for working due to medical issues [44], development of healthy animals is important when producing cloned working dogs. We have cloned various types of working dogs at the Customs Border Control Training Institute, the Korean National Police Agency, the Animal and Plant Quarantine Agency, and the Army, and their birth weights and subsequent growth were evaluated by breed (Labrador Retriever, German Shepherd, Springer Spaniel, and Belgian Malinois). The slightly higher birth weights of cloned working dogs (Labrador Retriever, n = 23, 500 g; German Shepherd, n = 11, 560 g; Springer Spaniel, n = 9, 600 g; Belgian Malinois, n = 4, 580 g; Fig. 1, unpublished data) compared to those of dogs produced naturally [16] might be due to the lower average litter size in pregnancies derived by transfer of cloned embryos compared to pregnancies produced by artificial insemination [34]; regardless, the cloned dogs showed normal growth patterns. Park *et al*. [45] also reported that growth profiles, as assessed by body weight and height, of three cloned Afghan hounds were similar to that of their cell donor. In addition, they confirmed that hematologic and serum biochemical values of young (7–12 weeks old) and young adult (35 weeks old to 1 year old) clones were within the reference ranges [45]. Neurological development of adult cloned working dogs (Labrador Retriever, n = 1; German Shepherd, n = 2; Belgian Malinois, n = 1) and their cell donors has been evaluated by performing physical and neurological examinations [26]. All examined dogs showed normality in posture, body position at rest, gait, identification of abnormal involuntary movement (tremors, tics, myoclonus, etc.) postural reactions (proprioceptive positioning, hopping reaction, wheelbarrowing, extensor postural thrust, hemistanding, and hemiwalking), cranial nerve assessments (palpebral reflex, corneal reflex, vestibular-ocular reflex, menace response, response to nasal stimulation, pupillary light reflex and gag reflex), spinal reflexes, and sensory evaluation.

Working dogs require exercise, conditioning, and physical fitness to maintain their athletic performance level [47] and, especially military or police dogs, are often exposed to stressful or threatening environments during their tasks [15,20]. Normal and healthy cardiovascular function is important to working dogs, but there have been reports about abnormal cardiovascular function in other cloned animals, such as pulmonary hypertension and right-sided heart failure in cloned calves [9,17] and sheep [11,49], and left- and right-sided heart abnormalities in cloned piglets [9]. However, until now, there have been no reports on cardiovascular analyses of working dogs, although echocardiographic parameters of seven cloned beagles were within normal reference ranges, indicating normal anatomy and cardiac function [60].

Temperaments of Working Dogs and Behavioral Similarities of Clones

The half of conventionally bred dogs that failed training as a working dog has been due to behavior-related issues [44], although some researchers believe the behavioral causes of failure (behavioral wastage) can exceed half of all trained dogs [3]. An individual dog's behavior and its response to environmental situations are influenced by its temperament [27,38], and a dog can present aspects of its future behavior during the socialization period (3–12 weeks) [50]. Among the temperament characteristics of dogs, Campbell considered domination as a key early criterion to predict future behavior [1] and designed a test to evaluate the level of domination [21]. Based on the Campbell domination test, a puppy aptitude test (PAT) has been developed by adding obedience factors to the domination test [54].

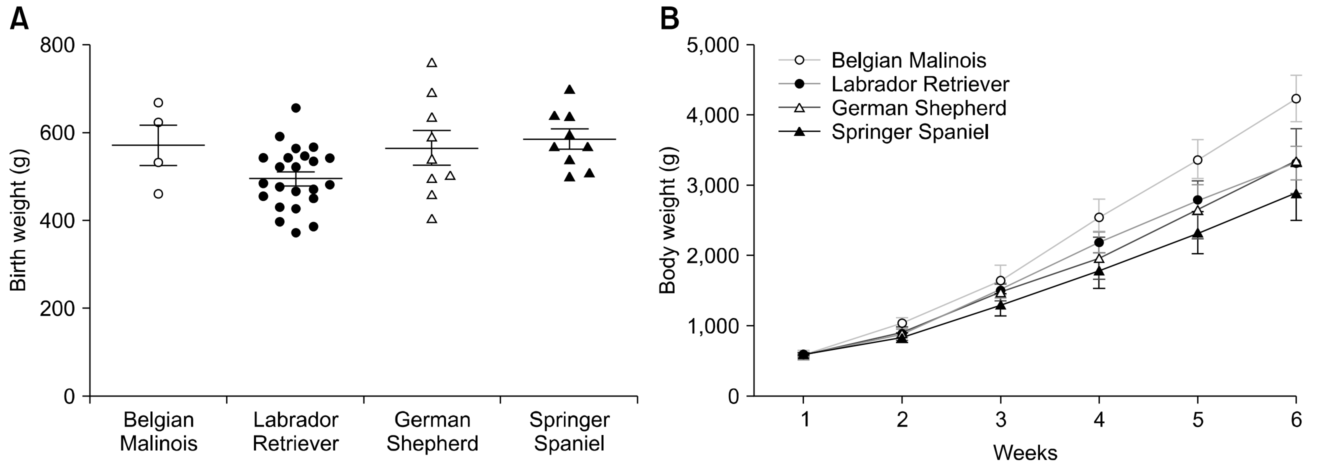

Fig. 1. Birth weight (A) and growth performance (B) of cloned working dogs from birth up to 6 weeks old. Cloned Belgian Malinois (○, n = 4), Labrador Retriever (●, n = 23), German Shepherd (△, n = 11), and Springer Spaniel (▲, n = 9) dogs were analyzed.

The Campbell test consists of five subtests related to social attraction, following, restraint, social dominance, and elevation dominance, and, based on the responses, the test results are scored as excessive dominance, dominance, balanced submission, submission, excessive submission, and independence [4]. According to Bartlett's interpretation [2], the subtest results can range from extremely dominant (Type 1) to independent and not affectionate (Type 5). Dogs exhibiting a Type 2 aptitude have an active and outgoing temperament, and, in general, are regarded as having the most appropriate aptitude type for working [2]. Dogs in Type 3 adapt well to changes and are also regarded as suitable working dogs. The Campbell test was used to evaluating temperaments of the six clones of an elite drug detection dog and of four control puppies delivered by natural breeding between elite drug detection male and female dogs [7]. The results showed that, while the average score of clones indicated a Type 2 aptitude, which was the most suitable for working at the Korea Customs Detector Dog Training Center, that of the control dogs indicated a Type 3 aptitude [7].

Interestingly, this observation is consistent with the PAT results and the results of the final selection tests for drug detection dogs. In 1979, Bartlett [2] established 10 subtests including social attraction, dominant or submissive tendency under stress, willingness to work with humans, and sensitivities based on the Campbell test. In 2001, Volhard and Volhard [54] divided the subtests into three categories, namely the pack drive (social attraction, following, and social dominance), fight-or-flight drive (restraint, elevation dominance, and stability), and prey drive (retrieving, sound sensitivity, and sight sensitivity), which are related to the dog's abilities to live in a group, run away, and hunt, respectively. The six drug-sniffing clones (excluding the one among seven that was hurt during training) and the four control dogs in the Korea Customs Detector Dog Training Center were subjected to PAT at ages 7 to 10 weeks and again at 16 weeks [6]. The tests revealed that the clones produced dominant behavior results in their average scores at 16 weeks that were consistent with those obtained at 7 to 10 weeks, whereas the control dogs did not produce consistent results [6]. In addition, the results of the final selection tests for drug detection dogs, which include five evaluation items (boldness, concentration, detecting process, response of detection and possessiveness), also showed that all of the clones passed the selection test and were subsequently selected as drug detection dogs, whereas only one of the control dogs passed and was selected [7]. The PAT has also been conducted on two cloned rescue dogs at the National 119 Rescue Headquarters, and both of them were classified as the same type and accepted humans and leaders easily [42].

Cloned dogs have identical genomes; similar to those observed in identical human twins. As reported in studies that have shown relationships between genes and cognitive abilities [5,41,53], results from a standardized behavioral test in Sweden using dogs at the Swedish Working Dog Association have revealed a shared genetic component associated with the dogs' behavioral traits [48]. In 2016, it was reported that learning, memory, and the exploratory patterns of six cloned beagles were more similar among them than among non-cloned control beagles [51]. Based on the results from the cloned drug detector dogs and the cloned beagles, it can be assumed that the temperaments of working dogs can be determined by genetic factors.

Concerns about Dog Cloning

Birth defects and lifespans of cloned animals have been the subjects of disputatious questions since the first cloned mammal, Dolly. Large offspring syndrome, including large size at birth, increased birth weight, breathing difficulties, reluctance to suckle, sudden perinatal death, and increased prenatal loss have been frequently reported in bovine and ovine cloned offspring [61]. However, in cloned dogs, features related to large offspring syndrome have been rarely reported with the exception of an increased placental weight [43]. Other perinatal abnormalities of cloned dogs have been reported [29,30], but the specific causes of these defects remain incompletely described. At present, reports on the lifespans and age-related diseases of cloned animals are rare, even though it has been almost 20 years since the first cloned mammals were produced. We recently reported on the lifespan of the world's first cloned dog, Snuppy, compared to that of its cell donor Tai [31]. Both were male Afghan hounds, and both Snuppy and Tai were diagnosed with cancer (T-cell lymphoma and hemangiosarcoma, respectively). Snuppy died when 10 years old during anticancer treatment, while Tai was euthanized when 12 years old at the request of the owner. Considering that the median age at death of Afghan hounds is 11.9 years old, it seems that cloned dogs have a life expectancy similar to that of non-cloned dogs.

Although all cloned dogs derived from an elite working dog can qualify as a working dog, the low efficiency of SCNT-based cloning could be a hurdle when propagating qualified working

Table 2. Reproductive efficiency in the cloning of working dogs

No. of pregnant/ recipient (%)	No. of delivered pups/embryos transferred (%)	No. of pups dying before 1 month old	Reference
4/18 (22.2)	11/400 (2.8)	1*	[43]
1/5 (20.0)	2/74 (2.7)	0	[30]
2/9 (22.2)	5/132 (3.8)	1	[29]
1/8 (12.5)	4/130 (3.1)	0	[35]
2/7 (28.6)	2/120 (1.7)	0	[42]

*Fetal death.

dogs. There have been efforts to improve dog cloning efficiency by applying mineral treatments to oocyte-donor dogs [33], as well as through acetylation [32] or synchronization of donor cells [43], replacement of primary culture media [28] or post-activation media [42], and by establishing a monitoring method during parturition [34]. However, the pregnancy rate (number of pregnant dogs divided by the number of recipients) and delivery rate (number of pups divided by number of embryos transferred) have been reported as 12.5% to 28.6% and 1.7% to 3.8% (Table 2), respectively, which are deemed unsatisfactory. For the practical application of dog cloning in the propagation of elite working dogs, as well as to reduce the number of experimental animals and the associated ethical concerns, the current low cloning efficiency needs to be improved; further research is needed.

Conclusion

Dog cloning technology has been applied to propagate working dogs (drug detection dogs, police dogs, quarantine dogs, rescue dogs, etc.) as well as cancer-sniffing dogs. Cloned working dogs have similar anatomical, physiological, neurological, and growth characteristics, as well as similar behavioral patterns, as those of their cell donors. In addition, it appears that cloned dogs can have similar lifespans to those of naturally bred dogs. Therefore, it can be concluded that qualified elite working dogs can be produced by cloning a working dog that exhibits both an appropriate temperament and good health. Research to improve dog cloning efficiency should be undertaken to expand the practical applications of this promising technology.

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Conflict of Interest

The authors declare no conflicts of interest.

References

1. **Asher L, Blythe S, Roberts R, Toothill L, Craigon PJ, Evans KM, Green MJ, England GCW.** A standardized behavior test for potential guide dog puppies: methods and association with subsequent success in guide dog training. J Vet Behav 2013, **8**, 431-438.
2. **Bartlett M.** A novice looks at puppy aptitude testing. Am Kennel Gaz 1979, 31-42.
3. **Branson N, Cobb M, McGreevy P.** Australian working dog survey report 2009. Australian Government Department of Agriculture, Fisheries and Forestry, Canberra, 2010.
4. **Campbell WE.** A behavior test for puppy selection. Mod Vet Pract 1972, **12**, 29-33.
5. **Cheung CH, Wood AC, Paloyelis Y, Arias-Vasquez A, Buitelaar JK, Franke B, Miranda A, Mulas F, Rommelse N, Sergeant JA, Sonuga-Barke EJ, Faraone SV, Asherson P, Kuntsi J.** Aetiology for the covariation between combined type ADHD and reading difficulties in a family study: the role of IQ. J Child Psychol Psychiatry 2012, **53**, 864-873.
6. **Choi J, Kim HB, Kang YU, Kim MJ, Lee SI, Oh HJ, Kim GA, Jo YK, Park EJ, Park JY, Choi YG, Lee BC.** Personality consistency analysis in cloned quarantine dog candidates. Acta Vet Brno 2017, **86**, 273-283.
7. **Choi J, Lee JH, Oh HJ, Kim MJ, Kim GA, Park EJ, Jo YK, Lee SI, Hong DG, Lee BC.** Behavioral analysis of cloned puppies derived from an elite drug-detection dog. Behav Genet 2014, **44**, 68-76.
8. **Choi YB, Kim GA, Oh HJ, Kim MJ, Jo YK, Setyawan EM, Lee SH, Lee BC.** Cloning of the short-tailed Gyeongju Donggyeong dog via SCNT: conserving phenotypic inheritance. J Vet Med Sci 2016, **78**, 329-331.
9. **Cibelli JB, Stice SL, Golueke PJ, Kane JJ, Jerry J, Blackwell C, Ponce de León FA, Robl JM.** Cloned transgenic calves produced from nonquiescent fetal fibroblasts. Science 1998, **280**, 1256-1258.
10. **Cornu JN, Cancel-Tassin G, Ondet V, Girardet C, Cussenot O.** Olfactory detection of prostate cancer by dogs sniffing urine: a step forward in early diagnosis. Eur Urol 2011, **59**, 197-201.
11. **Denning C, Burl S, Ainslie A, Bracken J, Dinnyes A, Fletcher J, King T, Ritchie M, Ritchie WA, Rollo M, de Sousa P, Travers A, Wilmut I, Clark AJ.** Deletion of the alpha(1,3)galactosyl transferase (*GGTA1*) gene and the prion protein (*PrP*) gene in sheep. Nat Biotechnol 2001, **19**, 559-562.
12. **Ehmann R, Boedeker E, Friedrich U, Sagert J, Dippon J, Friedel G, Walles T.** Canine scent detection in the diagnosis of lung cancer: revisiting a puzzling phenomenon. Eur Respir J 2012, **39**, 669-676.
13. **Ennik I, Liinamo AE, Leighton E, van Arendonk J.** Suitability for field service in 4 breeds of guide dogs. J Vet Behav 2006, **1**, 67-74.
14. **Foyer P, Bjällerhag N, Wilsson E, Jensen P.** Behaviour and experiences of dogs during the first year of life predict the outcome in a later temperament test. Appl Anim Behav Sci 2014, **155**, 93-100.
15. **Foyer P, Svedberg AM, Nilsson E, Wilsson E, Faresjö Å, Jensen P.** Behavior and cortisol responses of dogs evaluated in a standardized temperament test for military working dogs. J Vet Behav 2016, **11**, 7-12.
16. **Groppetti D, Pecile A, Palestrini C, Marelli SP, Boracchi P.** A national census of birth weight in purebred dogs in Italy. Animals 2017, **7**, 43.
17. **Hill JR, Winger QA, Long CR, Looney CR, Thompson JA, Westhusin ME.** Development rates of male bovine nuclear transfer embryos derived from adult and fetal cells. Biol

Reprod 2000, **62**, 1135-1140.
18. **Hong SG, Jang G, Kim MK, Oh HJ, Park JE, Kang JT, Koo OJ, Kim DY, Lee BC.** Dogs cloned from fetal fibroblasts by nuclear transfer. Anim Reprod Sci 2009, **115**, 334-339.
19. **Horvath G, Andersson H, Paulsson G.** Characteristic odour in the blood reveals ovarian carcinoma. BMC Cancer 2010, **10**, 643.
20. **Horváth Z, Igyártó BZ, Magyar A, Miklósi Á.** Three different coping styles in police dogs exposed to a short-term challenge. Horm Behav 2007, **52**, 621-630.
21. **Hvozdík A, Kottferová J, Alberto J, Ondrašovič M.** Test of social dominance in dogs. Veterinarski Arhiv 2003, **73**, 237-246.
22. **Issel-Tarver L, Rine J.** The evolution of mammalian olfactory receptor genes. Genetics 1997, **145**, 185-195.
23. **Jang G, Hong SG, Kang JT, Park JE, Oh HJ, Park CK, Ha JH, Kim DY, Kim MK, Lee BC.** Conservation of the Sapsaree (*Canis familiaris*), a Korean Natural Monument, using somatic cell nuclear transfer. J Vet Med Sci 2009, **71**, 1217-1220.
24. **Jang G, Hong SG, Oh HJ, Kim MK, Park JE, Kim HJ, Kim DY, Lee BC.** A cloned toy poodle produced from somatic cells derived from an aged female dog. Theriogenology 2008, **69**, 556-563.
25. **Jang G, Kim MK, Oh HJ, Hossein MS, Fibrianto YH, Hong SG, Park JE, Kim JJ, Kim HJ, Kang SK, Kim DY, Lee BC.** Birth of viable female dogs produced by somatic cell nuclear transfer. Theriogenology 2007, **67**, 941-947.
26. **Jeffery N.** Neurological examination of dogs 1. Techniques. In Practice 2001, **23**, 118-130.
27. **Jones AC, Gosling SD.** Temperament and personality in dogs (*Canis familiaris*): a review and evaluation of past research. Appl Anim Behav Sci 2005, **95**, 1-53.
28. **Kim GA, Oh HJ, Kim MJ, Jo YK, Choi J, Kim JW, Lee TH, Lee BC.** Effect of primary culture medium type for culture of canine fibroblasts on production of cloned dogs. Theriogenology 2015, **84**, 524-530.
29. **Kim MJ, Kang SC, Kim JH, Oh HJ, Kim GA, Jo YK, Choi J, Kim H, Lee YH, Yoo JM, Eom KD, Lee BC.** Ectopic liver and gallbladder in a cloned dog: possible nonheritable anomaly. Theriogenology 2015, **84**, 995-1002.
30. **Kim MJ, Oh HJ, Kim GA, Jo YK, Choi J, Kim HJ, Choi HY, Kim HW, Choi MC, Lee BC.** Reduced birth weight, cleft palate and preputial abnormalities in a cloned dog. Acta Vet Scand 2014, **56**, 18.
31. **Kim MJ, Oh HJ, Kim GA, Setyawan EMN, Choi YB, Lee SH, Petersen-Jones SM, Ko CJ, Lee BC.** Birth of clones of the world's first cloned dog. Sci Rep 2017, **7**, 15235.
32. **Kim MJ, Oh HJ, Kim GA, Suh HN, Jo YK, Choi YB, Kim DH, Han HJ, Lee BC.** Altering histone acetylation status in donor cells with suberoylanilide hydroxamic acid does not affect dog cloning efficiency. Theriogenology 2015, **84**, 1256-1261.
33. **Kim MJ, Oh HJ, Park JE, Kim GA, Park EJ, Jang G, Lee BC.** Effects of mineral supplements on ovulation and maturation of dog oocytes. Theriogenology 2012, **78**, 110-115.
34. **Kim MJ, Oh HJ, Park JE, Kim GA, Park EJ, Jo YK, Lee BC.** Duration of gestation in pregnant dogs carrying cloned fetuses. Theriogenology 2013, **79**, 257-260.
35. **Kim MJ, Park JE, Oh HJ, Hong SG, Kang JT, Rhim SH, Lee DW, Ra JC, Lee BC.** Preservation through cloning of superior canine scent detection ability for cancer screening. J Vet Clin 2015, **32**, 352-355.
36. **Lee BC, Kim MK, Jang G, Oh HJ, Yuda F, Kim HJ, Hossein MS, Kim JJ, Kang SK, Schatten G, Hwang WS.** Dogs cloned from adult somatic cells. Nature 2005, **436,** 641.
37. **Lee JB, Park C;** Seoul National University Investigation Committee. Molecular genetics: verification that Snuppy is a clone. Nature 2006, **440**, E2-3.
38. **Maejima M, Inoue-Murayama M, Tonosaki K, Matsuura N, Kato S, Saito Y, Weiss A, Murayama Y, Ito SI.** Traits and genotypes may predict the successful training of drug detection dogs. Appl Anim Behav Sci 2007, **107**, 287-298.
39. **Mazzone PJ.** Analysis of volatile organic compounds in the exhaled breath for the diagnosis of lung cancer. J Thorac Oncol 2008, **3**, 774-780.
40. **McCulloch M, Jezierski T, Broffman M, Hubbard A, Turner K, Janecki T.** Diagnostic accuracy of canine scent detection in early-and late-stage lung and breast cancers. Integr Cancer Ther 2006, **5**, 30-39.
41. **Miller G, Zhu G, Wright MJ, Hansell NK, Martin NG.** The heritability and genetic correlates of mobile phone use: a twin study of consumer behavior. Twin Res Hum Genet 2012, **15**, 97-106.
42. **Oh HJ, Choi J, Kim MJ, Kim GA, Jo YK, Choi YB, Lee BC.** Propagation of elite rescue dogs by somatic cell nuclear transfer. Anim Sci J 2016, **87**, 21-26.
43. **Oh HJ, Hong SG, Park JE, Kang JT, Kim MJ, Kim MK, Kang SK, Kim DY, Jang G, Lee BC.** Improved efficiency of canine nucleus transfer using roscovitine-treated canine fibroblasts. Theriogenology 2009, **72**, 461-470.
44. **Olson PN, Hall MF, Peterson JK, Johnson GS.** Using genetic technologies for promoting canine health and temperament. Anim Reprod Sci 2004, **82-83**, 225-230.
45. **Park JE, Kim MK, Kang JT, Oh HJ, Hong SG, Kim DY, Jang G, Lee BC.** Growth and hematologic characteristics of cloned dogs derived from adult somatic cell nuclear transfer. Cell Reprogram 2010, **12**, 141-150.
46. **Park JE, Oh HJ, Hong SG, Kim MJ, Kim GA, Koo OJ, Kang SK, Jang G, Lee BC.** Effective donor cell fusion conditions for production of cloned dogs by somatic cell nuclear transfer. Theriogenology 2011, **75**, 777-782.
47. **Robbins PJ, Ramos MT, Zanghi BM, Otto CM.** Environmental and physiological factors associated with stamina in dogs exercising in high ambient temperatures. Front Vet Sci 2017, **4**, 144.
48. **Saetre P, Strandberg E, Sundgren PE, Pettersson U, Jazin E, Bergström TF.** The genetic contribution to canine personality. Genes Brain Behav 2006, **5**, 240-248.
49. **Schnieke AE, Kind AJ, Ritchie WA, Mycock K, Scott AR, Ritchie M, Wilmut I, Colman A, Campbell KH.** Human factor IX transgenic sheep produced by transfer of nuclei from transfected fetal fibroblasts. Science 1997, **278**, 2130-2133.
50. **Scott JP, Fuller JL.** Genetics and the social behavior of the dog. University of Chicago Press, Chicago, 2012.
51. **Shin CW, Kim GA, Park WJ, Park KY, Jeon JM, Oh HJ, Kim MJ, Lee BC.** Learning, memory and exploratory similarities in genetically identical cloned dogs. J Vet Sci 2016, **17**,

563-567.
52. **Sonoda H, Kohnoe S, Yamazato T, Satoh Y, Morizono G, Shikata K, Morita M, Watanabe A, Morita M, Kakeji Y, Inoue F, Maehara Y.** Colorectal cancer screening with odour material by canine scent detection. Gut 2011, **60**, 814-819.
53. **van Soelen IL, Brouwer RM, van Leeuwen M, Kahn RS, Hulshoff Pol HE, Boomsma DI.** Heritability of verbal and performance intelligence in a pediatric longitudinal sample. Twin Res Hum Genet 2011, **14**, 119-128.
54. **Volhard J, Volhard W.** Dog training for dummies. John Wiley & Sons, New York, 2010.
55. **Walker DB, Walker JC, Cavnar PJ, Taylor JL, Pickel DH, Hall SB, Suarez JC.** Naturalistic quantification of canine olfactory sensitivity. Appl Anim Behav Sci 2006, **97**, 241-254.
56. **Walker JC, Hall SB, Walker DB, Kendal-Reed MS, Hood AF, Niu XF.** Human odor detectability: new methodology used to determine threshold and variation. Chem Senses 2003, **28**, 817-826.
57. **Williams H, Pembroke A.** Sniffer dogs in the melanoma clinic? Lancet 1989, **1**, 734.
58. **Willis CM, Church SM, Guest CM, Cook WA, McCarthy N, Bransbury AJ, Church MR, Church JC.** Olfactory detection of human bladder cancer by dogs: proof of principle study. BMJ 2004, **329**, 712.
59. **Wilmut I, Schnieke AE, McWhir J, Kind AJ, Campbell KH.** Viable offspring derived from fetal and adult mammalian cells. Nature 1997, **385**, 810-813.
60. **Yeo JH, Kim JH, Kim SY, Lee SJ, Park NW, Oh HJ, Kim MJ, Kim GA, Jo YK, Lee BC, Eom K.** Echocardiographic evaluation of cardiovascular function in cloned dogs. J Vet Clin 2015, **32**, 301-307.
61. **Young LE, Sinclair KD, Wilmut I.** Large offspring syndrome in cattle and sheep. Rev Reprod 1998, **3**, 155-163.