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Review Article

반려견 개량을 위한 유전적 잠재성 기반 주요 질병 및 양적 형질 조사

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Investigation of major canine diseases and quantitative traits based on estimation of genetic potential for dog breeding

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ABSTRACT

In this review paper, we investigated canine diseases and quantitative traits based on estimation of genetic potential to improve the quality of the companion dog breeding industry, as dogs make up the majority of companion animal. Until now, studies on the use of DNA markers in dogs have largely been related to parentage, breed identification, genetic diseases, and quantitative traits. Testing for parentage and breed often utilizes microsatellite markers, a method which has been shown to be effective in a number of studies. Genetic diseases in dogs are often caused by single mutations which show Mendelian inheritance. Causal genes, mutation types, and inheritance types have mainly been investigated in dog genetic diseases that occur most frequently. The coat color and body size of dogs are quantitative traits and do not follow Mendelian inheritance. The coat color of dogs is determined by a complex mechanism involving the interaction of 5 loci (*E*, *A*, *K*, *D*, and *B*). Body size was found to be related to mutations located in 17 genes (*ESR1*, *FGF4*, *STC2*, *SMAD2*, *HMGA2*, *GHR*, *R3HCM1*, *ADAMTS9*, *ACSL4*, *IGF1R*, *LCORL*, *IRS4*, *IGSF1*, *TBX3*, *MED13L*, *RNFT2*, and *IGF1*) and 2 loci (*ZNF608* and *IGF2BP2* loci). In addition, the hair feature is controlled by combinations of alleles at 5 genes (*FGF5*, *RSPO2*, *KRT71*, *FOXI3*, and *SGK3*). Overseas, companies (Embark, Wisdom panel, Orivet, etc.) that provide breed identification and screening for genetic diseases through DNA analysis are already available. Typical services include breed identification covering 180 − 250 breeds and risk diagnosis of 140 − 180 genetic diseases. DNA analysis services in the Republic of Korea are relatively inferior in quality/quantity and are under publicized. Therefore, it is necessary to develop a dog DNA analysis system that is easy to access and suitable for customers.

Key words: DNA marker, dog, dog industry, genetic disease, quantitative trait

INTRODUCTION

In the Republic of Korea, family size is gradually decreasing because of nuclear family structures becoming more common, an increase in one-person households, low fertility rates, and an aging population. The demand for companion animals and the related market are expected to grow steadily in order to alleviate alienation/loneliness and is estimated to expand to around 5.3 billion US dollars by 2020 (Hwang and Kim, 2013). Along with this growing trend, awareness of accepting companion animals as one of the family is also rising, and diversification and enhancement

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of companion animal related products and services is increasingly required from consumers.

Recent research has been conducted on the use of DNA markers for the identification and mapping of genetic diseases and quantitative phenotypic traits in various animals (Kim et al., 2009; Lim et al., 2018; Mealey et al., 2001; Newton et al., 2000). The development of DNA analysis technology services for these traits will contribute significantly to the development of the companion animal industry as a whole.

Therefore, we present this review on DNA research related to parentage tests, breed identification, genetic diseases, and quantitative phenotypic traits in dogs, as dogs make up the majority of companion animals, and propose ways to utilize DNA information to improve the quality of the companion dog industry by identifying trends in DNA analysis domestically and abroad.

PARENTAGE TEST AND BREED IDENTIFICATION

In the past, parentage testing and breed identification relied on visual methods, but modern developments in molecular biology mean accurate and scientific parentage testing and breed identification can be performed using DNA analysis. Microsatellites, also called short tandem repeats (STRs), are sequences found distributed across the entire genome, consisting of a variable number of repetitions of a DNA motif. Microsatellite markers are widely used in parentage testing and breed identification because they are polymorphic due to the difference in the number of repetitions in each individual (Richard et al., 2008). The effectiveness of this technique in determining dog's parentage was verified by identifying uncertain parenthood in dogs using microsatellite markers in the Republic of Korea and abroad (Binns et al., 1995; Chae et al., 1998; Chae et al., 1999; Kim et al., 2000; Ichikawa et al., 2001; DeNise et al., 2004; Kang et al., 2009). When attempting to identify the breed of dogs, it was reported that 414 dogs belonging to 85 breeds were distinguished with 99% accuracy using 96 microsatellite markers in a study carried out outside of the Republic of Korea (Parker et al., 2004).

GENETIC DISEASES

Genetic diseases in dogs have been influenced by a high preference for purebred dogs and excessive breed subdivision. As the risk of inbreeding increased, various diseases appeared and became increasingly frequent. Many of the genetic diseases known to date are caused by a single mutation in the genomic sequence, so the traits are passed on to the next generation according to Mendel's law. On the OMIA website (https://www.omia.org/home), a total of 841 disorders have been identified and 323 disorders following Mendelian rules with causal variants are summarized (assessed in May 2022). We focused on the most frequently occurring genetic diseases in dogs, together with details about the causal mutations and inheritance types (Table 1). It consists of 16 genetic diseases separated into 9 categories: clinical, hormones, eyes, kidney & bladder, brain & spinal cord, heart, muscular, metabolic, and skeletal. Most of these diseases are known to be caused by missense point mutations or indels (insertion or deletion) leading to frameshift mutations; however, some are caused by other types of mutations. One-third of the incidences of muscular dystrophy are known to be caused by the exon 7 of *DMD* being skipped due to a single point mutation located at the 3′ consensus splice site of intron 6, resulting in termination of the reading frame in exon 8 (Sharp et al., 1992). Osteogenesis imperfecta has been reported to be caused by a frameshift mutation, in which specific CTGA nucleotides located in exon 51 of *COL1A2* are replaced with TGTCATTGG (Campbell et al., 2001). The majority of reported dog genetic diseases have been identified as recessive, suggesting that there are more unaffected carriers than individuals with diseases.

Table 1. The dog's genetic diseases in which mutation is known

Category	Disease	Chr	Gene	Breed	Mutation	Inheritance type	Reference
Clinical	Drug Sensitivity	14	*MDR1*	Many breeds	Deletion	Codominant	Mealey et al. (2001), Neff et al. (2004), Barbet et al. (2009), Gramer et al. (2011)
Hormones	Congenital Hypothyroidism	17	*TPO*	Tenterfield Terrier	Missense	Recessive	Dodgson et al. (2012)
Eyes	Hereditary Cataracts, Early-Onset Cataracts, Juvenile Cataracts	5	*HSF4*	Staffordshire Bull Terrier, Boston Terrier	Insertion	Recessive	Mellersh et al. (2006)
		5	*HSF4*	Australian Shepherd	Deletion	Dominant	Mellersh et al. (2006)
	Primary Open Angle Glaucoma	20	*ADAMTS10*	Norwegian Elkhound	Missense	Recessive	Ahonen et al. (2014)
		20	*ADAMTS10*	Beagle	Missense	Recessive	Kuchtey et al. (2011)
		20	*ADAMTS17*	Basset Hound, Basset Fauve de Bretagne	Missense	Recessive	Oliver et al. (2015)
Kidney & Bladder	2,8-Dihydroxyadenine (2,8-DHA) Urolithiasis	5	*APRT*	Native American Indian Dog	Missense	Recessive	Furrow et al. (2014)
	Hyperuricosuria and Hyperuricemia or Urolithiasis	3	*SLC2A9*	Many breeds	Missense	Recessive	Bannasch et al. (2008), Karmi et al. (2010), Donner et al. (2016)
Brain & Spinal cord	Shaking Puppy Syndrome, X-Linked Generalized Tremor Syndrome	X	*PLP*	English Springer Spaniel	Missense	X-Linked Recessive	Nadon et al. (1990)
	Hypomyelination and Tremors	15	*FNIP2*	Weimaraner	Deletion	Recessive	Pemberton et al. (2014)
	Benign Familial Juvenile Epilepsy, Remitting Focal Epilepsy	3	*LGI2*	Lagotto Romagnolo	Missense	Recessive	Seppälä et al. (2011)
	Degenerative Myelopathy	31	*SOD1*	Many breeds	Missense	Recessive	Awano et al. (2009), Shelton et al. (2012), Capucchio et al. (2014)
Heart	Dilated Cardiomyopathy	14	*PDK4*	Dobermann	Deletion	Dominant	Meurs et al. (2012)
Muscular	Muscular Dystrophy	X	*DMD*	Cavalier King Charles Spaniel	Missense	X-Linked Recessive	Walmsley et al. (2010)
		X	*DMD*	Pembroke Welsh Corgi	Insertion	X-Linked Recessive	Smith et al. (2011)
		X	*DMD*	Golden Retriever	Splice site	X-Linked Recessive	Sharp et al. (1992)
	Myotonia Congenita	16	*CLCN1*	Miniature Schnauzer	Missense	Recessive	Rhodes et al. (1999)
		16	*CLCN1*	Australian Cattle Dog	Insertion	Recessive	Finnigan et al. (2007)
Metabolic	Malignant Hyperthermia	1	*RYR1*	Mixed breed	Missense	Dominant	Roberts et al. (2001)
Skeletal	Osteogenesis Imperfecta, Brittle Bone Disease	14	*COL1A2*	Beagle	Frameshift	Dominant	Campbell et al. (2001)
		21	*SERPINH1*	Dachshound	Missense	Recessive	Drögemüller et al. (2009)
		9	*COL1A1*	Golden Retriever	Missense	Dominant	Campbell et al. (2000)
	Oculoskeletal Dysplasia 1, Dwarfism-Retinal Dysplasia 1	24	*COL9A3*	Labrador Retriever	Insertion	Recessive	Goldstein et al. (2010)

QUANTITATIVE PHENOTYPIC TRAITS

The coat color and body size of dogs are examples of quantitative phenotypic traits. Table 2 indicates the genes related to the coat color and body size of dogs.

Table 2. The dog's quantitative traits in which the mutation is known

Category	Trait	Chr	Gene/locus	Reference
Coat color	Mask, Grizzle, Recessive Red	5	*MC1R*	Schmutz et al. (2003), Dreger and Schmutz (2010)
	Dominant Black	16	*CBD103*	Candille et al. (2007)
	Agouti, Sable	24	*ASIP*	Berryere et al. (2005)
	Dilute, Blue, Fawn	25	*MLPH*	Drögemüller et al. (2007)
	Brown, Chocolate, Liver, Red	11	*TYRP1*	Schmutz et al. (2002)
Body size	Height	1	*ESR1*	Plassais et al. (2019)
		18	*FGF4 retrotransposon*	Hayward et al. (2016), Plassais et al. (2019)
		4	*STC2*	Rimbault et al. (2013), Hayward et al. (2016), Plassais et al. (2019)
		7	*SMAD2*	Rimbault et al. (2013), Hayward et al. (2016), Plassais et al. (2019)
		10	*HMGA2*	Rimbault et al. (2013), Hayward et al. (2016), Plassais et al. (2019)
		4	*GHR*	Rimbault et al. (2013), Hayward et al. (2016), Plassais et al. (2019)
	Weight	11	*ZNF608 locus*	Plassais et al. (2019)
		19	*R3HCM1*	Plassais et al. (2019)
		20	*ADAMTS9*	Plassais et al. (2019)
		34	*IGF2BP2 locus*	Hayward et al. (2016), Plassais et al. (2019)
		X	*ACSL4*	Plassais et al. (2017), Plassais et al. (2019)
		3	*IGF1R*	Hoopes et al. (2012), Rimbault et al. (2013)
	Height, Weight	3	*LCORL*	Hayward et al. (2016), Plassais et al. (2019)
		X	*IRS4*	Plassais et al. (2017), Plassais et al. (2019)
		X	*IGSF1*	Plassais et al. (2017), Plassais et al. (2019)
		26	*TBX3*	Hayward et al. (2016), Plassais et al. (2019)
		26	*MED13L*	Hayward et al. (2016), Plassais et al. (2019)
		26	*RNFT2*	Hayward et al. (2016), Plassais et al. (2019)
		15	*IGF1*	Sutter et al. (2007), Rimbault et al. (2013), Hayward et al. (2016), Plassais et al. (2019)
Hair	Fur length	32	*FGF5*	Parker et al. (2017)
	Furnishing	13	*RSPO2*	Parker et al. (2017)
	Curl	27	*KRT71*	Parker et al. (2017)
	Hairless	17	*FOXI3*	Parker et al. (2017)
		29	*SGK3*	Parker et al. (2017)

Many studies have been conducted on coat color in dogs, because coat color is highly diverse in dogs relative to other animals (Schmutz and Berryere, 2007). The coat color of animals is determined through the complex interaction of allelic and non-allelic genes. In most vertebrate animals, differences in pigmentation arise from differences in two types of melanin – eumelanin and pheomelanin – which are determined by the *E* locus of *MC1R* and *A* locus of *ASIP*. However in dogs, in addition to the *E* locus and *A* locus, the *K* locus of *CBD103* is known to have a strong effect on determining the pigment type (Candille et al., 2007). The *E* locus of *MC1R* has four alleles: E^m (dominant eumelanin masked), E^g (dominant grizzle/domino), *E* (normal extension, no effect on phenotype), and *e* (recessive red), which shows dominance in the

order $E^g > E^m > E > e$ (Dreger and Schmutz, 2010; Schmutz et al., 2003). The *A* locus of *ASIP* also has four alleles: a^y (dominant sable), a^w (dominant agouti), a^t (dominant tan points), and *a* (recessive black), and shows dominance in the order $a^y > a^w > a^t > a$ (Berryere et al., 2005). The *K* locus of *CBD103* has three alleles: K^B (dominant black), k^{br} (dominant brindle), and k^y (recessive non-black), and shows dominance in the order $K^B > k^{br} > k^y$ (Candille et al., 2007). In addition, the *D* locus of *MLPH* is known to modulate the intensity of eumelanin expression through dilution caused by the recessive *d* allele (Drögemüller et al., 2007), and the *B* locus of *TYRP1* induces browning by modifying the molecule of eumelanin (Schmutz et al., 2002). Because the coat color of dogs is very diverse, there are still a number of traits for which the genetic basis of is unknown; therefore, further studies are necessary.

Dogs have varied body sizes, ranging from a very small body size like the Chihuahua to very large like the Great Dane. Unlike coat color, body size of dogs has been poorly studied. Studies have found associations between some loci and body size. For example, individuals with the *A* allele of a SNP in intron 2 of *IGF1*, the *A* allele of a SNP leading to a missense mutation in exon 2 of *IGF1R*, the *A* allele of a SNP located 20 kb downstream from *STC2*, a 9.9 kb deletion located 24 kb downstream from *SMAD2*, the *A* allele of a SNP located in the 5′ UTR of *HMGA2*, and the *A* and *T* alleles of 2 SNPs located in exon 5 of *GHR* have a significantly smaller body size (Hoopes et al., 2012; Rimbault et al., 2013; Sutter et al., 2007). Recently, many candidate genes and loci for morphological phenotypes were identified through the genome-wide association study (GWAS) based on next-generation sequencing (NGS) (Plassais et al., 2017; Plassais et al., 2019). The previously reported *IGF1*, *STC2*, *SMAD2*, *HMGA2*, and *GHR* were also significantly associated with height or weight phenotypes. Additionally, novel 12 genes (*ESR1*, *FGF4*, *R3HCM1*, *ADAMTS9*, *ACSL4*, *IGF1R*, *LCORL*, *IRS4*, *IGSF1*, *TBX3*, *MED13L*, and *RNFT2*) or 2 loci (*ZNF608* and *IGF2BP2* loci) were detected in height or weight. Moreover, phenotypes related to hair were confirmed using combinations of alleles at 5 genes (*FGF5*, *RSPO2*, *KRT71*, *FOXI3*, and *SGK3*) (Parker et al., 2017). The *FGF5* controls much of the fur length, *RSPO2* controls fur growth patterns or furnishings, *KRT71* contributes to hair curl, and *FOXI3* and *SGK3* generate hairlessness. Further studies are needed because very small or large breeds including unique features were often developed through intensive breeding and may therefore be associated with congenital genetic diseases.

TREND OF DOG DNA ANALYSIS

Breed identification and diagnostic services for genetic diseases in dogs using DNA analysis are offered by overseas companies such as Embark (www.embarkvet.com), Wisdom Panel (www.wisdompanel.com), and Orivet (www.orivet.com). Dog DNA analysis services initially sent consumers a swab-type kit to collect DNA from the dog's mouth, then consumers return the collected DNA to the analysis center. After that, the results are provided to consumers after breed identification and screening for genetic diseases has taken place. Although there are differences among companies, services usually include 180 to 250 breeds for breed identification and screening for between 140 and 180 genetic diseases. Some companies also offer health consulting for dogs based on the results of genetic diseases. Overseas, systematic dog DNA analysis services are well established and consumers also show high interest in these services. However, the domestic companion dog industry in the Republic of Korea lacks the overall quality and quantity of services for breed identification and screening for genetic diseases offered by DNA analysis, and publicity is also limited.

CONCLUSION

Dogs account for more than 70 percent of domestic companion animals, hugely affecting the industry in the Republic of Korea. While the industry has improved quantitatively in terms of diversity, improvement to the quality of related products and services for consumers have been limited. Testing for parentage, breed identification, and diagnosis of genetic diseases using DNA can be a positive method for improving

the quality of the companion dog industry. As the development of analysis services using DNA for dogs in the Republic of Korea is not as sufficient as it is abroad, it would be beneficial to develop and promote a DNA analysis system that is accessible to consumers and aims to enhance the quality of the companion animal industry domestically.

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