Review Article

Genes Associated with Genetic Diseases in Collies, Shetland Sheepdogs and Border Collies

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Abstract

Canine genetic disorders inherited through genes or chromosomes. Mutations can also occur spontaneously or influenced by environmental factors. Such disorders can be transmitted to offspring. However, the disease may not be developed owing to other influenced factors. Dominant and recessive genetic mechanisms also affect the trait outcome. This article discussed the abnormalities of genes affected by the disease and/ or genetic disorders in Collies, Shetland sheepdogs and Border collies, sharing the Collie lineage. Most of these disorders are caused by autosomal recessive genes. Hence, paired recessive alleles are required in order to express its phenotype. Although dogs are asymptomatic carriers, they can pass down defective genes to offspring. The first gene to be described was multi-drug resistance gene 1 (*MDR1*), which expresses P-glycoprotein, functioning to eliminate a number of drugs from the brain. The other genes included nonhomologous end joining (*NHEJ1*), retinal degeneration 3 (*RD3*) and ceroid lipofuscinosis neuronal 5 (*CLN5*) genes which are associated with Collie eye anomaly, rod-cone dysplasia and type 2 disease neuronal ceroid lipofuscinosis, respectively. Knowledge of genes associated with genetic diseases leads to the development of the DNA tests for early diagnosis and breed selection. This will help reduce the incidence of such disorders.

Keywords: Border Collie, Collie, dog, gene, genetic disorder, Shetland sheepdog

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Thai J Vet Med. 2011. 41(2): 135-142.

บทคัดย่อ

ยีนที่เกี่ยวข้องกับโรคทางพันธุกรรมในสุนัขพันธุ์คอลลี่ เช็ทแลนด์ชีพด็อก และบอร์เดอร์คอลลี่

กรรณาภรณ์ สุริยผล

ความผิดปกติทางพันธุกรรมเกิดขึ้นโดยการสืบทอดผ่านยีนหรือโครโมโซม แม้บางครั้งความผิดปกติดังกล่าวอาจเกิดขึ้นได้เองหรือเกิดขึ้นเนื่องจากอิทธิพลของสิ่งแวดล้อม ความผิดปกติทางพันธุกรรมสามารถถ่ายทอดไปสู่ลูกหลานได้ แต่อาจไม่ก่อให้เกิดโรค เนื่องจากปัจจัยด้านอื่นๆ ต่อตัวสัตว์ ลักษณะเด่นและลักษณะด้อยก็มีผลต่อการเกิดโรค ในบทความนี้ได้กล่าวถึงความผิดปกติของยีนที่มีผลก่อโรคและ/หรือความผิดปกติทางพันธุกรรมในสุนัขพันธุ์คอลลี่ เช็ทแลนด์ชีพด็อก และบอร์เดอร์คอลลี่ ซึ่งทั้งหมดเป็นสายพันธุ์สุนัขคอลลี่ ส่วนมากความผิดปกติดังกล่าวมักเป็นลักษณะด้อย นั่นคือสุนัขต้องได้รับยีนผิดปกติทั้งจากพ่อและแม่จึงจะแสดงอาการความผิดปกติ สุนัขที่เป็นพาหะแม้ไม่แสดงอาการแต่ก็สามารถถ่ายทอดยีนที่ผิดปกติไปสู่ลูกหลานได้ ยีนแรกได้แก่ multi-drug resistance gene 1 (*MDR1*) แสดงออกเป็น P-glycoprotein ซึ่งมีหน้าที่กำจัดยาหลายชนิดออกจากสมอง ยีนอื่นๆ คือ nonhomologous end joining (*NHEJ1*) retinal degeneration 3 (*RD3*) และ ceroid lipofuscinosis neuronal 5 (*CLN5*) ยีนดังกล่าวมีความสัมพันธ์กับโรค Collie eye anomaly โรค Rod-cone dysplasia type 2 และโรค neuronal ceroid lipofuscinosis ตามลำดับ ความรู้เรื่องยีนที่เกี่ยวข้องกับโรคทางพันธุกรรมนำมาสู่การพัฒนาวิธีวินิจฉัยโรคตั้งแต่แรกเริ่ม ทำให้เกิดการคัดเลือกสายพันธุ์ ซึ่งจะช่วยลดอัตราการเกิดความผิดปกติดังกล่าวได้

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Introduction

A genetic disorder is an abnormal condition that is inherited through genes or chromosomes. Abnormalities may be due to different forms of genes (gene variation) or an alteration of genes (gene mutation). They can be due to one gene or a group of genes. Several genetic disorders are inherited, but some spontaneous mutations or mutations due to environmental exposure are also observed. These mutations can be passed down through families to future generations. However, in some cases an individual that has an inherited disorder may never develop the disease because additional genetic changes or environmental factors are required. Since the first draft of the dog genome sequence was unveiled in 2004 (Lindblad-Toh et al., 2005), the role of genes in diseases has better been understood. Genetic factors have been shown to play an important role in congenital malformations [e.g.cleft palate (Richtsmeier et al., 1994), deafness (Famula et al., 2007; Sommerlad et al., 2010)], metabolic disorders [e.g.exocrine pancreatic insufficiency (Clark et al., 2005), diabetes mellitus (Mori et al., 2009; Seddon et al., 2010; Short et al., 2010), phosphofructokinase deficiency (Giger et al., 1985; Giger et al., 1986), pyruvate kinase deficiency (Whitney et al., 1994; Skelly et al., 1999)], inherited immune disorders [e.g.complement deficiency (Johnson et al., 1986; Ameratunga et al., 1998), cyclic hematopoiesis (Benson et al., 2003), severe combined immunodeficiency (Felsburg et al., 1998; Felsburg et al., 1999)] and cancer [e.g. canine mammary tumor (Gotoh et al., 2006; Kim et al., 2010; Klopfleisch et al., 2010), thyroid carcinoma (Devilee et al., 1994), multifocal renal cystadenocarcinoma and nodular dermatofibrosis (Lingaas et al., 2003; Bonsdorff et al., 2008)].

The frequency of inherited disorders can be decreased through breed selection. The dog genome is composed of 78 chromosomes, in 39 pairs, in which approximately 100,000 genes are located (Lindblad-Toh et al., 2005). One half of a chromosome pair comes from each parent. A gene at the same locus on a matching chromosome is called an allele and each individual has 2 alleles per genetic position. When 2 alleles are identical, showing normal or disorder (e.g. AA or aa, respectively), the individual is homozygous wild-type or homozygous mutant at that locus, respectively, but if the alleles are different (Aa), then the individual is heterozygous mutant (Lodish et al., 2008).

For the recessive trait, the offspring requires 2 copies of a recessive mutated gene from both parents to develop diseases which are called autosomal recessive. But if the offspring receives only one copy of a recessive mutated gene (Aa), then it is a carrier that will not develop the disease but the carrier

can pass it on to the next generation. When both parents are carriers, then there is a 1 in 4 chance that the offspring will inherit both mutated gene copies and develop the disease. If one parent is a carrier and the other is homozygous recessive, there is 50% chance that the offspring will also be affected with the disease (Table 1). For a dominant trait, only 1 copy is required to express the trait. Hence, either AA or Aa can express the characteristic. In several cases, however, there is incomplete dominance or autosomal dominant disorders with incomplete penetrance, showing variable expressivity in the trait. Hence, although both parents are affected and all puppies have a susceptibility to the disorder, not all will be affected equally. For example, if penetrance is 80%, only about 80% of the pups which inherit the mutated gene will express it.

In some cases, polygenic inheritance is found. Polygenic traits are controlled by several genes. The gene expression is influenced by several factors, including gender, nutrition, breed, etc. Heritability varies among different breeds and different populations of a particular breed (Strachan and Read, 1999). A classic example of a polygenic trait in dogs is canine hip dysplasia which is a common inherited, polygenic, non-congenital malformation of the hip joint. Affected animals are born with normal hips but during the period of fastest growth (usually between the 4th and 10th months) develop subluxation of the femoral head and degenerative joint disease (Priester and Mulvihill, 1972; Mackenzie et al., 1985). Linked quantitative trait loci (QTL) and eventually single nucleotide polymorphism (SNP) genotyping were used to identify genetic markers associated with the disease as a haplotype block (Todhunter et al., 1999; Chase et al., 2004; Chase et al., 2005; Janutta et al., 2006; Zhu et al., 2009). However, as a polygenic trait, canine hip dysplasia is caused by the interaction of several genes and environmental factors such as nutrition which can alter the gene expression and, hence, change the manifestations and severity of the disease (Fries and Remedios, 1995).

Table 1 Expected results of breeding strategies for autosomal recessive diseases

Genotype	Parent 2		
Parent 1	Normal	Carrier	Affected
Normal	All = Normal	1/2 = Normal 1/2 = Carriers	All = Carriers
Carrier	1/2 = Normal 1/2 = Carriers	1/2 = Normal 1/2 = Carriers 1/2 = Affected	1/2 = Carriers 1/2 = Affected
Affected	All = Carriers	1/2 = Carriers 1/2 = Affected	All = Affected

X-linked trait is another common inherited disease. The gene is located on the X chromosome. Male puppies have one X chromosome from their mother whereas female puppies have two X chromosomes, one from their mother and the other from their father. Hence, male puppies that receive a defective recessive gene from their mother will develop the disease whilst under the same situation female puppies will be merely unaffected carriers unless their father also carries the defective gene. Owing to a much larger size of X chromosomes than Y chromosomes, there are more X-linked traits than Y-linked traits. Some canine X-linked diseases can be good models for diseases in humans such as canine X-linked muscular dystrophy (CXMD) which was first described in the Golden Retriever (Cooper et al., 1988). The clinical signs and pathology in dogs are similar to Duchenne muscular dystrophy in humans. Sex-linked muscular dystrophy in dogs has been reported to be associated with dystrophin deficiency. Spontaneous mutations of the dystrophin gene, which functions to stabilize the muscle membrane during contraction, have been found predominantly in male dogs (Walmsley et al., 2010; Smith et al., 2011).

From all of that mentioned above, knowledge of genetic diseases and of ways to recognize affected animals or carriers of the disease early are important in reducing inherited disorders. Many diseases do not show signs or symptom until the late onset of a dog's life or after dogs are bred. Hence, DNA tests are useful for 1) dog owners to know how to bring up their dogs properly, 2) veterinarians to help in diagnosing and prescribing therapy, 3) dog breeders and potential dog owners to avoid problems when choosing a pet and to avoid defective genes in their lines of dogs. In this review, the disorders of genes reported to be directly associated with diseases in Collies, Shetland sheepdogs and Border Collies will be mentioned, including Multidrug resistance (MDR1-in Collies and Shelties), Collie eye anomaly or choroidal hypoplasia (CEA-in Collies and Border Collies), rod-cone dysplasia type 2 (rcd2 – in Collies) and neuronal ceroid lipofuscinosis (NCL-in Border Collies). Candidate genes associated with the disease and can be used in DNA-based tests will be presented.

1. Multidrug resistance 1 (MDR1)

Collies and Collie lineage breeds are likely to face serious side effects from certain drug administration like ivermectin than other breeds. The cause of this sensitivity is due to a 4 base deletion of the multi-drug resistance gene 1 or the *ATP*-binding cassette protein subfamily B1 (*MDR1* or *ABCB1*) (Mealey et al., 2001). This gene encodes a multidrug resistance protein, P-glycoprotein (P-gp). The P-gp functions as an *ATP*-dependent drug-efflux pump at the blood-brain barrier, transporting a variety of drugs such as ivermectin from the brain back into the blood (Kim et al., 1998; Jonker et al., 1999). The *MDR1*

gene is composed of 28 exons and located on chromosome 7 with 209 kb in length. The gene mutation reveals an exonic 4-bp deletion (AGAT) at nucleotide position 230 of the *MDR1* open reading frame that creates a nonsense frame shift at amino acid position 75 followed by a premature stop codon, resulting in the production of a nonfunctional fragment of the P-gp protein (Mealey et al., 2001; Nelson et al., 2003; Roulet et al., 2003). Hence, dogs that have a mutated *MDR1* gene will have less capacity to eliminate P-gp substrate drugs compared to others. A number of drugs routinely used in veterinary medicine are P-gp substrates and have been shown to cause problems in dogs with a mutated *MDR1* gene such as antiparasitic agents (ivermectin), gastrointestinal agents (loperamide) and anticancer agents (vincristine, vinblastine, doxorubicin) (Mealey et al., 2003; Sartor et al., 2004; Dowling, 2006). Exposure to these drugs may result in serious neurological signs such as hypersalivation, ataxia, blindness, tremor, respiratory distress and even death. A number of dog breeds reported to be affected by *MDR1* mutation include Collies, Border Collies, Shetland Sheepdogs (Paul et al., 1987; Tranquilli et al., 1991; Hopper et al., 2002; Yas-Natan et al., 2003). Homozygous recessive dogs display dose related toxicity as ivermectin-sensitive phenotypes. Heterozygous mutated dogs can be carriers of the defect gene allele to offspring. Although they appear to be clinically normal, the transporter function is probably compromised as demonstrated by the bone marrow toxicity induced by vincristine and doxorubicin in a heterozygous Collie (Mealey et al., 2003).

2. Collie Eye Anomaly (choroidal hypoplasia)

Collie Eye Anomaly (CEA) or Choroidal Hypoplasia (CH) is a recessively inherited eye disorder, causing abnormal development of the choroid under the retina of the eye (Yakely et al., 1968). The choroid appears pale and thin, almost transparent, and the blood vessels of the choroid can easily be recognized with an ophthalmoscope in those areas. In mild disease, choroidal thinning is the only detectable abnormality and the dog retains normal vision. However, dogs with mild disease can produce severely affected offspring. In severe cases, colobomas are seen around the optic nerve head. This can lead to secondary complications such as partial or complete retinal detachment and/or abnormal blood vessel growth with hemorrhage. Consequences are that either one eye or both eyes can be affected. This could happen in 5-10% of dogs with CEA/CH, normally by 2 years of age. Complications of severe cases can lead to blindness. The disease is seen not only in Collies but also in Shetland Sheepdogs, Border Collies, Australian Shepherds and Lancashire Heelers (Barnett and Stades, 1979; Bedford, 1982; Bedford, 1998; Munyard et al., 2007). There is no treatment for the disease. Since the clinical signs vary greatly among affected dogs, causing a difficult situation for the breeder, genetic testing will help avoid breeding carriers or affected dogs. Selective breeding against CEA markedly decreases the frequency of affected puppies (Yakely, 1972).

Mutation of the nonhomologous end joining factor 1 (*NHEJ1*) gene on canine chromosome number 37 has been reported to be associated with the disease. The mutation consists of the deletion of 7.8 kb (7799 bp) within the intron 4 in gene, comprising nucleotides 28,697,542-28,705,340 on chromosome 37 [based on the CanFam2 assembly (http://genome.ucsc.edu/)] and two additional noncoding SNPs at the CanFam2 locations 28,706,834 and 28,713,928 (Parker et al., 2007).

3. Rod-cone dysplasia type 2

Rod-cone dysplasia type 2 (*rcd2*) is one form of progressive retinal atrophy (PRA), which comprises a group of inherited diseases of the retina, causing gradual vision loss leading to blindness in several dog breeds (Ray et al., 1995; Aguirre et al., 1999; Miyadera et al., 2009) whereas *rcd2* segregates merely in rough and smooth collies. Due to retinal degeneration, affected dogs will develop an early onset of night blindness, typically apparent at 6 weeks of age. In most cases, dogs are completely blind at 1 year old. The disease is inherited as an autosomal recessive trait (Wolf et al., 1978). Hence, two copies of the mutation must be present in order to develop the disease and carriers that do not show the disease but are able to pass the disease down to offspring. The mutation of the *RD3* gene (initial name *C1orf36*) is found to cosegregate with *rcd2*. A 22 bp insertion (gcccgcccccgcccccgccccc) in one *RD3* splice variant in exon 4, which is missing in CanFam2.0, is identified and predicted to alter the normal open reading frame (ORF). The *rcd2* DNA test is able to identify with complete accuracy whether a dog is normal, a carrier or affected (Kukekova et al., 2009).

4. Neuronal Ceroid Lipofuscinosis

Neuronal ceroid lipofuscinosis (NCL or CLN) is a neurodegenerative disease found in dogs such as Border Collies and other animals. There is an abnormal accumulation of lysosomal storage bodies in the cells, leading to progressive neurodegeneration of the brain and eyes, severe neurological impairment and early death. Affected dogs appear normal at birth, but symptoms exhibits around 1-2 years of age. Due to the severity of the disease, affected dogs rarely survive beyond 3 years of age. NCL is a class of inherited neurological disorder and is inherited as an autosomal recessive trait (Studdert and Mitten, 1991). Dogs affected with NCL develop pathological degenerative changes in the central nervous system and fluorescent nerve cells when examined under blue or ultraviolet light (Taylor and Farrow, 1988). Neurological signs vary among breeds and can overlap with signs present in other neurological disorders. A mutation in CLN5 with a nonsense mutation (Q206X) within exon 4 is reported to be responsible for NCL in Border Collies (Melville et al., 2005). This truncation mutation also occurs in humans with a similar progression of the symptoms of the disease and similar ultrastructure patterns of subunit C of ATP synthetase within the lysosomes (Sohar et al., 1999). In both cases, as neurodegeneration increases, a range of physical and psychological symptoms appear, including changes in normal

sleeping patterns.

Conclusion

Knowledge of gene associated diseases is very useful to develop DNA diagnostic tests in the future. Not only affected dogs but also carriers can be diagnosed. Carriers, normally in much greater numbers than affected animals, express no symptoms of the disease, but are able to breed affected pups. Hence, such carriers should be excluded from the breeding population. Since genetic testing can be done at any ages, pups intended to be used for breeding should be DNA tested to determine whether they are carriers. Then genetic status of an individual can be known even before symptoms are displayed and a defective gene can probably be eliminated completely from their line.

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