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A review of hereditary diseases of the German shepherd dog

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Abstract The German shepherd dog (GSD) is a preferred choice of many law enforcement and military agencies across the world. Unfortunately, the breed is afflicted with approximately 50 hereditary diseases. Seven major diseases afflicting the GSD are described herein: pancreatic acinar atrophy, megaesophagus, hip dysplasia, degenerative myelopathy, hemophilia A, von Willebrand disease, and hereditary multifocal renal cystadenocarcinoma and nodular dermatofibrosis. Also included is a discussion of behavior, a characteristic thought to be inherited in the dog and often problematic in larger breeds such as the GSD. Current clinical and genetic research efforts pertaining to these diseases are reviewed.

Introduction

According to fossil and ancient art work, dogs and humans have shared a bond for nearly 140000 years (Coren, 1994; Lemish, 1996). Dogs serve in a multitude of roles, from companion and confidant to successful working dog. A working dog can be categorized into several different fields: military working dogs (MWD), law enforcement/drug dogs, service dogs, and dogs serving as a diagnostic tool for human medicine (Moody et al., 2006). Certain breeds of dog have shown greater aptitude for being a successful working dog, and among those is the GSD. The United States Department of Defense maintains a large number of MWD, with more than 1700 used for force-protection, security, and contraband detection in 2001 (Moore et al., 2001). Because of the extensive training, cost, and valuable role of these dogs, they are maintained to provide the highest quality of service for the longest period of time possible. The United States Department of Defense aims to extend the working careers of their dogs by providing the best veterinary care available and keeping extensive records that can be used for research (Moore et al., 2001). The GSD has also proven to be an invaluable breed for The Seeing Eye, Inc., leading this organization to establish its own breeding colonies of GSDs. They maintain extensive medical records on dogs and use this information to help in studies of hip dysplasia and other traits (The Seeing Eye, Inc., 2007).

There are over 400 recognized breeds of domestic dog, *Canis familiaris*, of which approximately half are estimated to be afflicted with hereditary diseases. The GSD is no exception, with over 50 hereditary disorders afflicting the breed (Table). Hereditary diseases, as well as behavioral problems, are often responsible for prematurely ending the career of a working dog (Moore et al., 2001). Additionally, the GSD was the third most registered breed in 2006,

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Table Mode of inheritance of the hereditary diseases that most commonly afflict the GSD

Inherited Diseases Found in the GSD	Mode of Inheritance	Inherited Diseases Found in the GSD	Mode of Inheritance
Acral lick dermatitis	Undetermined	Hip dysplasia	Polygenic
Aortic stenosis	Autosomal dominant in Newfoundlands	Hyperadrenocorticism	Undetermined
Atopic dermatitis	Autosomal dominant in human	Hypertrophic osteodystrophy	Undetermined
Autoimmune lymphocytic thyroiditis	Autosomal recessive in borzoi	Lymphedema	Autosomal dominant with variable expressivity in some breeds
Bladder stones	Autosomal recessive in Dalmatian, English bulldog, Newfoundland	Masticatory myositis	Undetermined
Calcinosis circumscripta	Undetermined	Megaesophagus	Undetermined
Cataracts	Undetermined for many breeds. Autosomal recessive, autosomal dominant, or with incomplete dominance	Mitral valve disease	Undetermined
Cerebellar abiotrophy	Autosomal recessive in border collie	Myasthenia gravis	Autosomal recessive
Cervical vertebral instability (wobbler syndrome)	Undetermined, thought to be autosomal recessive in the Great Dane, Doberman pinscher, and borzoi	Nodular dermatofibrosis	Autosomal dominant
Cleft lip/palate	Undetermined, thought to be autosomal recessive in the Brittany spaniel and autosomal dominant with incomplete penetrance in the English and French bulldog, pointer, and shih tzu	Optic nerve hypoplasia	Undetermined
Corneal dystrophy	Undetermined. Autosomal recessive with variable expressivity in Siberian husky and sex-linked in Airedales	Pannus	Undetermined
Cutaneous asthenia	Most forms appear autosomal dominant, although an autosomal recessive form likely occurs as well	Panosteitis	Undetermined
Cutaneous lupus erythematosus	Undetermined	Patent ductus arteriosus	Polygenic
Deafness	Undetermined	Pemphigus erythematosus	Undetermined
Degenerative myelopathy	Undetermined	Perianal fistula	Undetermined
Demodecosis	Undetermined	Persistent right aortic arch (vascular ring anomaly)	Polygenic
Dermatomyositis	Undetermined, thought to be autosomal dominant with variable expressivity	Progressive retinal atrophy	X-linked trait in Siberian husky. In most breeds, autosomal recessive.
Dermoids	Undetermined	Pulmonic stenosis	Undetermined
Elbow dysplasia	Polygenic	Retinal dysplasia	Autosomal recessive in many breeds, undetermined in others
Epilepsy	Undetermined	Sebaceous adenitis	Undetermined

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Table (*continued*)

Inherited Diseases Found in the GSD	Mode of Inheritance	Inherited Diseases Found in the GSD	Mode of Inheritance
Exocrine pancreatic insufficiency	Autosomal recessive	Seborrhea	Autosomal recessive trait in the West Highland white terrier and thought to be autosomal dominant inheritance with variable expressivity in other breeds
Familial vasculopathy	Thought to be autosomal recessive in GSD	Selective IgA deficiency	Undetermined
Footpad disorder	Undetermined	Small intestinal bacterial overgrowth	Undetermined
Gastric dilatation-volvulus	Undetermined	Tricuspid dysplasia	Undetermined
German shepherd pyoderma	Thought to be autosomal recessive	Vertebral stenosis (lumbosacral)	Polygenic
Glycogen storage disease type III	Autosomal recessive	Vitiligo	Undetermined
Hemivertebra	Autosomal recessive	von Willebrand's disease Type I	Thought to be an autosomal trait with incomplete dominance
Hemophilia	X-linked recessive	von Willebrand's disease Type II and III	Autosomal recessive

Source: Canine Inherited Disorders Database. Available at: http://www.upei.ca/cidd/breeds/germanshepherd2.htm Accessed December 20, 2007.

and owners are devastated when the life of their companion ends earlier then expected (American Kennel Club, 2007). Because GSDs hold such an important role in our lives, it is important to understand the hereditary diseases that most often afflict this breed. With the advancement in both genetics and medicine, hereditary diseases will be better understood and the ability to treat and prevent these diseases will be significantly improved. This review highlights several of the major hereditary diseases that commonly afflict the GSD, including pancreatic acinar atrophy (PAA), megaesophagus (ME), canine hip dysplasia (CHD), degenerative myelopathy (DM), hemophilia A, von Willebrand disease (vWD), and hereditary multifocal renal cystadenocarcinoma and nodular dermatofibrosis (RCND). In addition to these diseases, behavior is also discussed, as it can often affect the lifespan of a dog, in particular the GSD.

Pancreatic acinar atrophy

PAA is a gastrointestinal disease characterized by the selective atrophy of pancreatic acinar cells as a result of lymphocytic pancreatitis. PAA, the most common cause of exocrine pancreatic insufficiency (EPI) in the dog, commonly occurs in the GSD (Westermarck et al., 1993). During the initial stage of the disease, pancreatic tissues exhibit lymphocytic infiltration, dilation of the rough endoplasmic reticulum, fusion of zymogen granules, swollen mitochondria, and pyknotic nuclei (Westermarck et al., 1993). Histologic evaluation of pancreatic biopsy specimens from dogs with end-stage PAA reveals atrophy, scattering, and disorganization of acinar cells (Rogers et al., 1983; Westermarck et al., 1993). GSDs with PAA often have little identifiable pancreatic tissue at exploratory laparotomy or necropsy (DiMagno et al., 1973).

Clinical signs include a ravenous appetite, weight loss, and voluminous soft stools (Westermarck et al., 1989). Steatorrhea, borborygmus, coprophagia, and polydipsia are also associated with EPI (Raiha and Westermarck, 1989). Diagnosis of EPI is accomplished by measurement of serum cTLI, with severely decreased concentrations ($\leq$ 2.5 μg/L) being diagnostic for PAA (Westermarck et al., 1993). Affected dogs can be treated with pancreatic enzyme supplements, with a favorable prognosis for the vast majority of patients. Still, many dogs with EPI are euthanized because of poor treatment response or because their owners are unable to afford the enzyme supplements (Hall et al., 1991; Wiberg et al., 2002).

PAA is a disorder that is widespread in the GSD population, but also affects other breeds including the collie, Labrador retriever, and corgi. Ninety-six percent of affected dogs present with signs of EPI by 5 years of age, and many dogs show signs as early as 6 months (Raiha and Westermarck, 1989; Westermarck et al., 1993).

Previous studies have reported complex segregation analyses, suggesting that a single gene segregating in an

autosomal recessive fashion is causative for PAA (Moeller et al., 2003). These data were from 22 affected dogs from 2 unrelated pedigrees of GSDs. After publication of this report, a subset of dogs from 1 pedigree that did not possess any signs typical of EPI was identified. cTLI testing was repeated, and necropsy of 2 dogs was carried out to confirm that these dogs were affected with PAA. This variability in phenotype suggests that PAA may be a polygenic disorder.

Recent genetic studies of PAA have indicated a region of interest on canine chromosome 3 (CFA03) and eliminated *GP25L* as a candidate gene. A kindred of GSDs was genotyped for 384 microsatellite markers and a maximum 2-point lod score of 2.5 for marker FH2107 was identified on CFA03 (Clark et al., 2005). Lod scores are statistical measurements that are used to assess the likelihood of linkage of a marker to a disease gene, with a lod of 3 or greater indicating 1000:1 odds in favor of genetic linkage. A lod score between 2 and 3 is generally considered to be suggestive of linkage but not conclusive. Clark et al. also used an oligonucleotide array to generate gene expression profiles for normal and affected pancreata, which revealed 244 genes with greater than 2-fold difference in expression levels. One gene, *GP25L,* located on CFA03, was found to be down-regulated by more than 500-fold based on quantitative real-time PCR in affected pancreata and was further investigated as a candidate gene. Unfortunately, sequence data did not reveal a mutation in the coding sequence that segregates with PAA. *GP25L* was eliminated as a causative gene based on sequence data of coding regions and splice sites of the gene. There is a possibility that mutations may exist in the promoter or enhancer regions of *GP25L*; however, the identification of SNPs within the gene that do not segregate with the disease further supports the idea that *GP25L* does not harbor a mutation causative for PAA (Clark et al., 2005). Additionally, *CCKAR* and *CCK* were evaluated as causative for EPI in a Eurasian dog breed which has a clinical phenotype of EPI that is similar to that found in the GSD; however, these 2 genes were not evaluated in the GSD (Proschowsky and Fredholm, 2007). This analysis determined neither *CCKAR* nor *CCK* is causative for EPI in the Eurasian dog breed based on failure to find linkage to regions harboring these genes in the dogs evaluated. Neither of these analyses revealed a mutation causative for PAA, but specific genes that are involved in the disease were identified and potential causative genes were eliminated. Finally, other regions of interest in the genome were selected for future investigation.

Megaesophagus

Another gastrointestinal disorder that affects the GSD is congenital ME. ME occurs in puppies after weaning and is characterized by dilation and hypomotility of the esophagus. The result of these anomalies is regurgitation several minutes to hours after eating. Regurgitation episodes may occur as often as several times a day or as infrequently as once every few days. Affected puppies are malnourished, show a general failure to thrive, and are at risk for aspiration pneumonia.

Signs typically begin around 5 weeks after weaning onto solid food. Diagnosis of ME is achieved by standard X-rays and/or fluoroscopy (barium swallow) (Guilford, 1990). ME is sometimes diagnosed by the relative esophageal diameter; however, recent studies show that this method is limited in distinguishing dogs with ME resulting from myasthenia gravis from those with ME resulting from other causes (Wray and Sparkes, 2006). For genetic studies it is important that ME is not the result of another primary disease, so this should be considered when diagnosing dogs for studies. Congenital ME is typically treated by feeding a high-calorie liquid diet from a raised dish (Guilford, 1990). Mortality is high in affected neonates, but the condition usually resolves by 4 to 6 months of age in puppies that survive (Cox et al., 1980). Analyses of pedigrees of wire fox terriers and miniature schnauzers with ME have failed to conclusively identify the mode of inheritance, although autosomal recessive with incomplete penetrance or polygenic inheritance seem most likely (Osborne et al., 1967; Cox et al., 1980). It is not possible to identify carrier dogs prior to breeding.

Hip dysplasia

Canine hip dysplasia is one of the most commonly inherited joint diseases affecting large-breed dogs, and the secondary hip osteoarthritis results in pain and lameness. For dogs with hip dysplasia, the head of the femur and the acetabulum do not fit together correctly, resulting in painful and damaging friction (Lust, 1997). When a dog continues to bear weight on the hips, friction strains the joint capsule, which then damages the cartilage and leads to the release of inflammatory complexes within the joint. A vicious cycle arises of destruction of cartilage, inflammation, and pain, or, symptoms of osteoarthritis (Fries and Remedios, 1995; Farese et al, 1998; Burton-Wurster et al., 1999). Reports of dysplastic dogs also having other abnormal joints indicates that the primary defect is not restricted to the hips, but may be systemic (Olsewki et al., 1983; Farquhar et al., 1997; Kealy et al., 1997; Morgan et al., 1999).

The age of onset of arthritis, as well as the clinical signs, varies greatly among dogs. Some dogs may have genetic susceptibility but do not show a clinical phenotype (Willis, 1989). Hip dysplasia can be diagnosed through a variety of radiographic techniques. The traditional method positions a mature dog in dorsal recumbency, and a radiograph of the hip-extended ventrodorsal view is taken. This radiograph is then scored on a 7-point scale based on the degree of subluxation and secondary osteoarthritis (Henry, 1992; Mateescu et al., 2006). This 7-point scale ranges from excellent, fair, or good hip conformation to borderline,

moderate, or severe hip dysplasia. The signs of hip osteoarthritis that can be seen on radiographs include: flattening of the femoral head and acetabulum, subchondral bone sclerosis, and osteophytes on the acetabular rim and femoral neck (Mateescu et al., 2005). Other methods to assess hip joint conformation associated with hip dysplasia include: dorsolateral subluxation hip joint score, age at detection of femoral capital ossification, and distraction index (Madsen et al., 1991; Smith et al., 1993; Smith, 1997; Todhunter et al., 1997; Farese et al., 1998; Farese et al., 1999; Lust et al., 2001). Even with all of these different methods of evaluating the hips, there is still no method that is 100% sensitive and specific for diagnosing young dogs with hip dysplasia because it is a quantitative trait (Todhunter et al., 2003).

Treatment for hip dysplasia includes 2 surgical options: (1) the therapeutic option, which aims to treat and salvage the arthritic hip, including total hip replacement or femoral head osteotomy (Kim et al., 2005; Rawson et al., 2005); and (2) the prophylactic option, which usually is a triple pelvic osteotomy (Ocal and Sarierler, 2007). Some dogs respond well to surgery but, given with the cost, recovery time, and effects of surgery, it is sometimes not an option for owners. Nonsurgical methods of treatment include pain medications, anti-inflammatory medications, and physical therapy (Johnston, 1992; Millis and Levine, 1997). These methods also have limitations, and in some cases affected dogs are ultimately euthanized. Because hip dysplasia is so complex and devastating, many genetic studies have been conducted to try and help understand this disease.

Canine hip dysplasia is a complex trait with several major and many minor quantitative trait loci (QTL) interacting with environmental factors most likely responsible for the phenotype of the disease (Henricson et al., 1966; Leighton et al., 1977; Hedhammar et al., 1979; Mateescu et al., 2005). A study in 2004 showed that major genes contributed to hip dysplasia in a Finnish dog population (Mäki et al., 2004). Recently, a whole genome scan for QTL was performed in GSDs. At the genome-wide level of significance at $P < 0.05$, QTL for canine hip dysplasia were located on 9 different canine chromosomes: 1, 3, 4, 8, 9, 16, 19, 26, and 33 (Marschall and Distl, 2007). Future studies can aim to refine these map positions of QTL that were identified in the GSD. Although there is no genetic test for canine hip dysplasia, a study by Leighton showed that careful selective breeding may reduce the prevalence of hip dysplasia in lines and improve hip scores. In this study, the best parents for the next generation were chosen on the basis of estimated breeding values, which were calculated by combining observed values of individual dogs with known relationships in the population pedigrees. In fewer than 5 generations of selection, the percentage of GSDs with canine hip dysplasia at 12 to 16 months of age decreased from 55 to 24% (Leighton 1997). Leighton's study further exemplifies the importance of careful breeding by informed breeders on the overall health of the breed.

Degenerative myelopathy

DM is a slow, progressive neurodegenerative disease first described by Averill in 1973. DM is reported to affect several breeds such as the Siberian husky and Pembroke Welsh corgi, but it is most prevalent in the GSD population (Bichsel and Vandevelde, 1983; Coates, 2005). DM is characterized by a loss of proprioceptive function, which progresses to ataxia and weakness of the pelvic limbs. In many dogs, the first visible clinical signs are dragging of the hind paws, crossing of the legs while standing, and a general inability to sense the position of the rear end. Symptoms of DM worsen, either steadily or in phases, over time and eventually there is complete paralysis of the rear end. Atrophy of the caudal trunk and pelvic limbs is often evident as the disease progresses (Barclay and Haines, 1994). Reports from some cases indicate DM may progress up the spinal cord and cause forelimb weakness and even difficulties with respiration (Barclay and Haines, 1994). Age of onset is 9 years on average but ranges between 5 and 14 years of age (Averill, 1973). Nutritional and exercise regimens may slow progression, but there is no treatment or cure for this devastating disease, and euthanasia is usually necessary within several months of the onset of clinical signs (Johnston et al., 2000). Recent studies showed that dogs receiving intensive physiotherapy have longer ($P < 0.05$) survival time (mean 255 days), as compared to dogs with moderate ($n = 6$; mean 130 days) or no ($n = 7$; mean 55 days) physiotherapy. This study also found that affected dogs receiving physiotherapy remained ambulatory longer then those that did not receive physical treatment, highlighting the importance of physiotherapy for affected dogs (Kathmann et al., 2006).

Unfortunately, necropsy is the only method available to definitively diagnose DM. As such, a diagnosis is made only when radiographs and myelograms rule out other spinal cord trauma, intervertebral disc protrusion, lumbosacral stenosis, or cancer of the spinal cord. Necropsies of affected dogs reveal lesions in the white matter of the thoracolumbar spinal cord (Braund and Vandevelde, 1978). The lesions are restricted to white matter and are characterized by vacuolar spaces, which correlate to a loss of myelin, and large eosinophilic circular granular bodies, which represent axonal degeneration (Averill, 1973; Barclay and Haines, 1994). Although no analyses of inheritance have been published, DM does not appear to be a simple Mendelian trait.

Although the etiology and pathogenesis of this disease remain uncertain, there are 2 widely held hypotheses: (1) DM results from a vitamin B deficiency and (2) DM has an immune-mediated pathogenesis (Clemmons et al., 1989; Clemmons et al., 1991). Because vitamin B supplementation does not seem to help affected dogs and others have failed to find a reduction in urinary levels of B12 metabolites, it remains unproven that there is a link between vitamin B deficiency and DM (Averill, 1973; Griffiths

and Duncan, 1975; Braund and Vandevelde, 1978). Immunological findings in several studies have further supported that DM is an immune-mediated disease (Fechner et al., 2003). Williams et al. found that serum vitamin E levels are lower in DM-affected dogs (1985). In 2003, Fechner et al. analyzed the α-tocopherol transfer protein (αTtp) gene as a candidate gene for canine DM because vitamin E deficiency in humans results in a similar neurodegenerative disorder. Sequence and expression data eliminated αTtp as a possible candidate gene for canine DM (Fechner et al., 2003). To date, there is no trusted, definitive way to identify a GSD with DM.

Hemophilia A

Hemophilia A is a clotting disease that occurs in both the human and the dog, and it is the most commonly reported inherited blood clotting disorder in the dog. Hemophilia A exhibits considerable variation among affected individuals (Parry et al., 1988); however, all show decreased levels of Factor VIII. Factor VIII is a glycoprotein that is required for platelet adhesion to the wall of blood vessels during clotting, forming a bridge between fibrin and the site of vascular injury to initiate primary hemostasis (Lobetti and Dippenaar, 2000). Lack of Factor VIII results in the inability of fibrin to adhere to injury sites, thereby preventing clot formation. Affected individuals exhibit prolonged bleeding times, abnormal platelet retention, hematomas, excessive bruising, and mild to severe tendency to bleed (Dodds, 1975). Diagnosis of hemophilia A is made through quantification of blood clotting factors with the use of the activated partial thromboplastin time test. Gene therapy trials have demonstrated the efficacy of introducing Factor VIII into affected individuals to alleviate severe bleeding symptoms, however this treatment has not been widely used, because of the reduction of levels of Factor VIII within months following therapy (Connelly, et al., 1996; Brown, et al., 2003).

Canine hemophilia A is inherited in an X-linked recessive fashion. Most affected individuals are males, with carrier females typically producing 50% affected male offspring and 50% carrier female offspring (Tennant, 1996). In the GSD, the widespread propagation of a mild form of hemophilia A was traced back many generations to a single founder male (Brooks, 1999). In a colony of dogs in Canada, hemophilia A arises from aberrant splicing and premature termination of transcription of the Factor VIII gene, which results in a polyadenylated transcript lacking exons distal to 22 and terminating with a novel sequence element (Hough et al., 2002). This mutation has not been found to be causative for hemophilia A in the GSD.

Hemophilia A symptoms can be alleviated with the administration of recombinant Factor VIII. Studies have shown that in vivo recombinant Factor VIII possesses full functional activity, binds to circulating von Willebrand factor (vWF), and exhibits normal recovery and survival characteristics (Giles et al., 1988). In addition, hemophilia A remains a hot candidate for gene therapy. Recent trials led to long-term transgene expression and vector persistence in 2 FVIII-deficient animals with conversion of their severe phenotype to a moderate one. Vector-associated toxicity remains a problem with gene therapy trials, so further studies are needed before this can be considered a safe treatment for hemophilia A (McCormack et al., 2006).

von Willebrand Disease

von Willebrand disease (vWD), first described as a bleeding disorder in the GSD in 1970, exhibits significant variation in different breeds of dog, and even within breeds, with respect to clinical presentation and severity (Lobetti and Dippenaar, 2000). Genetic heterogeneity of vWD results in different single mutations in almost every afflicted breed (Brooks, 1999). vWD is similar to hemophilia A in the dog, both of which are characterized by low levels of Factor VIII. However vWF additionally exhibits low to nonexistent levels of von Willebrand factor (Johnstone and Crane, 1981). Administering purified Factor VIII to dogs with vWD corrects the prolonged bleeding time, at first leading to the thought that vWF and Factor VIII are similar or identical (Bouma et al.,1975). vWF was later determined to be a large protein that prevents the degradation of Factor VIII in circulation, suggesting that the decrease in vWF may be associated with the low levels of Factor VIII in dogs with vWD (Lobetti and Dippenaar, 2000). Similar to hemophilia A, vWD is diagnosed through quantification of blood clotting factors with the use of the activated partial thromboplastin time test. Dogs with vWD exhibit reduced to absent levels of Factor VIII. Clinical signs may consist of bruising, mucosal bleeding, prolonged hemorrhage post-trauma or surgery, and long in vivo bleeding time (Brooks, 1999).

There are 3 types of vWD. In the most common, Type 1, the concentration of vWF is low with a normal multimeric pattern, and clinical signs are mild. Type 1 is thought to be inherited in an autosomal recessive fashion in some breeds and is thought to possibly be inherited in an autosomal dominant fashion with incomplete penetrance in other breeds (Venta et al, 2000). Type 1 may lead to serious bleeding problems, but it is generally the least severe of the 3 types (Venta et al., 2000). In Type 2, which is rare in the GSD, the large multimers of vWF are reduced to undetectable. Type 2 is inherited in an autosomal recessive fashion in the dog, in contrast to humans, where it is inherited in autosomal dominant fashion. Dogs affected with Type 2 have severe bleeding tendencies (Johnson et al., 1988; Brooks, 1992; Ruggeri and Ware, 1993; Brooks et al, 1996). In Type 3, the most severe form, the entire vWF is undetectable (Johnstone et al., 1993; Brooks et al., 1996; Moser et al., 1996; Slappendel et al., 1998; Johnstone and Norris, 1984). Type 3 is inherited in an autosomal

recessive fashion, and serious bleeding episodes of affected dogs require blood transfusions or cryoprecipitate to restore the missing vWF. Dogs that are heterozygous have moderately reduced factor concentrations but appear to have relatively normal homeostasis (Venta et al., 2000).

The causative mutation for vWD in several breeds has been determined, and PCR-based tests are available. Type 2 vWD was studied in a line of German shorthaired pointers in which some members had a nucleotide variant in exon 28 of the vWF gene. A PCR diagnostic test for the variant nucleotide was successfully used in these dogs to select and produce progeny that were variant free vWD free (Kramer et al., 2004). A single base deletion was found to be causative for vWD in the Scottish terrier (Venta et al., 2000). To date, the causative mutation for both hemophilia A and vWD in the GSD remain unknown.

Hereditary multifocal renal cystadenocarcinoma and nodular dermatofibrosis (RCND)

RCND, first described in 1985, is a hereditary cancer syndrome in the GSD. This cancer syndrome is characterized by firm nodules of dense collagen fibers in the skin and subcutis accompanied by bilateral, multifocal tumors in the kidneys. Additionally, every female that was examined at an appropriate age also presented with uterine leiomyomas, with 50% of dogs experiencing metastasis (Moe and Lium, 1997). Symptoms include hematuria and urinary retention, progressive weight loss, polydipsia, anorexia, vomiting, and respiratory distress.

There are a number of breed-associated cancers, such as gastric carcinoma in the chow chow (King, 2003), but RCND in the GSD is the only one that is well characterized genetically (Jonasdottir et al., 2000; Lingaas et al., 2003). This cancer syndrome was originally described in Switzerland in 1985, with subsequent reports from various countries (Suter et al., 1983). Previous familial studies of RCND indicate it is inherited in an autosomal dominant pattern (Lium and Moe, 1985; Moe and Lium, 1997). Recent genetic studies mapped the syndrome to canine chromosome 5 (Lingaas et al., 2003). This region in the dog overlaps a region in the human that harbors the human Birt-Hogg-Dubé (BHD) locus at 17p11.2 (Khoo et al., 2002). BHD is an autosomal dominant renal carcinoma syndrome in the human and is phenotypically similar to RCND in the dog. The BHD gene, also known as FLCN, encodes the folliculin protein, and has been found to cause Birt-Hogg-Dubé syndrome when mutated. Screening of the canine genome with sequence of the human BHD gene revealed portions of the orthologous canine BHD gene. These portions were subsequently sequenced and revealed a disease-associated mutation in exon 7 that confers an amino acid change in a highly conserved region of BHD (Lingaas et al., 2003). Also, studies show that the RCND mutation may have a homozygous lethal effect (Lingaas et al., 2003). A recent study by Bonsdorff et al. demonstrated that skin tumors of RCND-affected dogs may be caused by haploinsufficiency of the FLCN gene product, describing the situation where an individual has only 1 functional copy of a gene, the other inactivated by mutation. However, many cancers are characterized by mutations in multiple genes, increasing in frequency with advancing age. According to the multimutation theory in cancer by Nordling, carcinogenesis is the result of multiple mutations, or hits, in the genome, with greater frequencies of cancers occurring with greater numbers of hits (Nordling, 1953). Interestingly, second-hit mutations in FLCN of dogs with RCND were detected in 71% of the kidney tumor samples studied, suggesting a tumor suppressor function of FLCN in RCND (Bonsdorff et al., 2008).

Behavioral conditions

An overview of GSDs would not be complete without mention of behavior, one of the most common areas of misconception regarding GSDs. As previously mentioned, the GSD is a working breed that is often used in police and military service. Studies on the cause of both discharge from service and death of military working dogs differed in the percentages of GSDs that were eliminated from service, ranging from only 2% euthanized as a result of behavior (Moore et al., 2001) to 20%-88% (Evans et al., 2007). The inability of owners to provide adequate training and activity for GSDs often leads to behavior problems brought on by boredom and loneliness. Additionally, a naturally high prey drive leads to GSDs erroneously being classified as aggressive, even by some veterinarians, who have suggested that aggression may be inherited by some breeds, including GSDs (Fox, 1970; Caldwell and Little, 1980). Several studies have reported high prevalence of dog bites from GSDs (Beck et al., 1975; Szpakowski et al., 1989); however, a study by Overall and Love showed that because GSDs are the most popular breed (pure or mixed breed) they appear in, but are not actually overrepresented in, dog bite cases (2001).

Canine behavior is an intriguing topic because the behavior of a dog greatly affects the role that dog will fill in society. For example, working dogs are often selected based on certain behavioral characteristics such as self-confidence, nerve stability, temperament, and fighting drive. There are various standardized tests that can be used by breeders and/or trainers to score the temperament of dogs, but these methods leave room for inconsistencies and biases (Ruefenacht et al., 2002; Fuchs et al., 2005). However, the Swedish Working Dog Association has carried out a standardized behavioral test for almost 20 years called the Dog Mentality Assessment (DMA) test, which has proven to have a high test–retest consistency (Svartberg et al., 2005) and a good predictive power for behaviors

outside the test situation and for performance in working dog trials (Svartberg, 2002; Svartberg, 2005). A recent study has shown that behavior is a heritable trait (Saetre et al., 2006). In this study, 16 behavioral traits were investigated in the GSD and the Rottweiler. It was concluded that there is substantial shared genetics underlying most of the behavioral responses in all of the test situations, with the exception of aggression. Aggression was shown to be genetically correlated across 2 test situations; however, there was a weak correlation to the other behavioral traits. Thus, the existence of a genetically determined broad behavioral trait can explain a significant part of the behavioral response in all the test situations except aggression. The work by Svartberg (2002) indicated that the broad personality trait predisposes a dog to trainability and that the boldness score predicts the behavioral response of a dog in the home (Svartberg, 2005). There are several early studies that agree with Saetre et al. (2006) indicating the existence of a broad personality trait in the dog similar to the shyness–boldness dimension described by Svartberg and Forkman (2002) (Scott and Fuller, 1966; Goddard and Beilharz, 1985; Wilsson and Sundgren, 1997; Saetre et al., 2006).

Further investigation into the genetics of canine behavior may lead to the identification of genes responsible for specific behaviors. Certain behavioral disorders such as thunderstorm phobia can be extremely detrimental. Many dogs injure themselves, escape, or are destructive during storms. These dogs are often also sensitive to any loud noise, which would be problematic for working dogs. Interestingly, studies have shown there is a breed predisposition for thunderstorm phobia. The phobia occurs more often in dogs from the herding group than dogs from any other group (McCobb et al., 2001). One hypothesis to this occurrence is that herding dogs are generally bred to be more reactive and to suppress aspects of their predatory drive (McCobb et al., 2001). Overall et al. (2001) determined that there is an association between separation anxiety, noise phobia, and thunderstorm phobia. There is a high probability that a dog with thunderstorm phobia is also highly likely to suffer from separation anxiety. Likewise, there is an even higher probability that a dog with noise phobia would also suffer from separation anxiety. Interestingly, the probability that a dog would suffer from noise phobia if it had thunderstorm phobia was higher than the converse of the situation. This study indicated that dogs suffering from any of these conditions should be screened for the remaining since there is such a strong correlation between them. In treating dogs suffering from these conditions, it is important to note the interactions among these conditions to effectively manage the dog (Overall et al., 2001). The behaviors discussed above are often classified as part of canine compulsive disorder (CD), a syndrome believed to be caused by stress, conflict, or frustration (Hewson et al., 1999). Physical manifestations of canine CD can include spinning, tail chasing, persistent licking, and unprovoked aggression (Luescher, 2000). GSDs are among the breeds most likely to have acral lick dermatitis (lick granuloma), caused by persistent licking of, typically, the paws or flank, resulting in thickened, ulcerated sores often requiring medical treatment. Lick granuloma is thought to result from boredom or psychological stimuli and has been proposed to be a reliable animal model of human obsessive-compulsive disorder (Rapoport et al., 1992). The identification of genes responsible for any of these behaviors discussed would be of great importance to the health and manageability of GSDs.

Conclusion

The majority of the inherited diseases in the GSD still lack reliable methods for identifying affected or carrier dogs prior to breeding. Without proper tests for these hereditary diseases, dogs are unknowingly bred before symptoms arise, thereby propagating the deleterious alleles throughout subsequent generations. Because the GSD is afflicted with many hereditary diseases and serves such an important role in our daily lives, it is important to continue to study these diseases in the GSD. This importance is exemplified by the grants the Canine Health Foundation continues to award to laboratories studying the hereditary diseases of the GSD. The identification of a causative gene for any of these diseases would have a huge effect on the GSD breed. By identifying affected dogs at an early age, breeders can use this information to plan proper and safe breedings, thus leading to a healthier population of GSDs. Although genetic tests are still lacking for this breed, informed breeders can help improve the health of the breed by "phenotypically testing" dogs prior to breeding. Dogs with clinical signs such as excessive bruising or prolonged clotting times should not be bred for possibility of passing on hemophilia A or vWD to future generations. Breeders should be able to phenotypically identify dogs with poor hips prior to breeding and remove these dogs from the breeding pool. Leighton (1997) proved that with cautious and informed breeding, the health of future generations can be greatly improved. With continued research, more genetic tests will be developed, which in addition to conscientious breeding will make the GSD a healthier and more efficient breed.

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