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Survey of Canine Monogenetic Diseases with Established Molecular Bases

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Received: August 10, 2014; Accepted: September 09, 2014; Published: September 11, 2014

Abstract

The development of a dog breed often involves selection, which intentionally propagates valued genetic traits. Unfortunately, untoward traits can be collateral propagated during this process. For the purpose of identifying trends in canine genetic diseases, we examined 36 randomly chosen canine pathologies involving single gene mutations. For each disease we provide a brief summary of breed predilection, clinical signs, the underlying genetic mutation, and the availability of a commercial diagnostic test. The following trends were noted in this non-exhaustive list of diseases. First, these genetic diseases primarily involve the ophthalmic (28%) and nervous systems (28%). Second, no single breed was over-represented in these genetic diseases. Third, the majority (89%) of the mutations involve coding regions of the respective genes. Fourth, most (78%) mutations were autosomal recessive. Fifth, nucleotide substitutions were the most common mutation (42%). Finally, genetic testing is available for 89% of these diseases. This review encapsulates canine pathologies associated with single genetic defects, thus providing a resource for practitioners and researchers.

Keywords: Canine; Genetics; Single nucleotide polymorphisms

Introduction

Genetics of the domestic dog (Canis familiaris) are heavily influenced by humans, as we select for traits deemed beneficial to owners of these companion animals. These traits include property surveillance, adaptation to adverse weather conditions, hunting prowess, herding, and the ability to pull carts and sleds. In order to expedite the amplification of these traits, inbreeding is a frequent phenomenon used in dog breeding throughout the world. A potential consequence of this selection process is the propagation of undesirable traits that can be cryptic for generations. Recognition of the inheritance of undesirable traits is an important consideration for dog breeders and veterinarians. Herein we provide an overview of 36 canine genetic diseases in which a single gene underlies a condition specific to a breed or a small subset of breeds. These 36 diseases were chosen randomly based on the search terms “canine genetic diseases”, trends in canine genetic diseases, we examined 36 randomly chosen canine pathologies involving single gene mutations. For each disease we provide a brief summary of breed predilection, clinical signs, the underlying genetic mutation, and the availability of a commercial diagnostic test. The following trends were noted in this non-exhaustive list of diseases. First, these genetic diseases primarily involve the ophthalmic (28%) and nervous systems (28%). Second, no single breed was over-represented in these genetic diseases. Third, the majority (89%) of the mutations involve coding regions of the respective genes. Fourth, most (78%) mutations were autosomal recessive. Fifth, nucleotide substitutions were the most common mutation (42%). Finally, genetic testing is available for 89% of these diseases. This review encapsulates canine pathologies associated with single genetic defects, thus providing a resource for practitioners and researchers.

Cerebellar ataxia in Finnish hounds

In this early onset disease, dogs display ataxia and tremors ultimately resulting in unorthinness. In Finnish Hounds the disease is linked to a homozygous T >C missense mutation in SEL1L, resulting in a Ser658Pro substitution in SEL1L. SEL1L is a component of the endoplasmic reticulum-associated protein degradation complex, and the dysfunction of this protein causes endoplasmic reticulum stress [3].

CNS hypomyelination and congenital goiter in the toy fox and rat terriers

Toy Fox and Rat Terriers are prone to an autosomal recessive disease involving CNS hypomyelination and congenital goiter. Affected animals have dysphagia, generalized neurologic signs, fuzzy coat with no guard hairs, delayed growth, dullness and listlessness, abnormal gait, and enlarged thyroid glands. These animals have no functional thyroid peroxidase due to a nonsense mutation involving a cytosine to thymine transition in exon 3 of the gene encoding this enzyme. Thyroid peroxidase is needed for the iodination of tyrosine residues on thyroglobulin, and this enzyme is needed for myelination especially in the corpus callosum. The dual function of this enzyme underlies the duality of the clinical signs noted in this disease [4].

C3 Deficiency in Brittany spaniels

Cataracts in Australian shepherds

Cataracts are the leading cause of hereditary blindness in dogs, with over 100 breeds affected. For a number of breeds, this disease is autosomally recessive and is based on a single nucleotide polymorphism (insertion) in exon 9 of the HSF4 gene. HSF4 encodes for heat-shock factor 4, a transcription factor critical to lens development [1]. In Australian Shepherds, however, hereditary cataracts are due to an autosomal dominant single nucleotide deletion in exon 9 of HSF4. This deletion results in a frame-shift mutation leading to the incorporation of 86 incorrect amino acids in HSF4, thus abrogating the ability of HSF4 to act as an appropriate transcription factor in lens development. In Australian Shepherds, the lack of HSF4 activity leads to posterior polar subcapsular cataracts in both eyes, with a varying onset dependent upon the number of alleles bearing the HSF4 1-bp deletion [2].
C3 deficiency results in nephropathy and diminished immunologic responses to bacterial infections. In Brittany Spaniels, the disease has been associated with a deletion of a cytosine in exon 17 that results in a premature stop codon. This deletion abrogates the function of C3, thus predisposing the animal to bacterial infections normally addressed by the C3 protein [5].

**Cone-rod dystrophy in Irish Glen of Imaal Terriers**

Cone-rod dystrophy is a progressive degeneration of the retina that leads to blindness. In the Irish Glen of Imaal Terrier, this disease is autosomally recessive and is based on a large deletion on chromosome 16. This deletion eliminates exons 15 and 16 of the ADAM9 gene that encodes for a disintegrin/metalloprotease-like protein [6]. This deletion results in a frame-shift mutation leading to a premature stop codon that truncates 285 amino acids from the carboxyl-terminal end of the protein. The functional absence of this protein leads to dysplasia of photoreceptor outer segments in the apical microvilli of retinal pigment epithelium. Ophthalmologic examination can detect the degeneration at about 15 months of age [7].

**Copper toxicity in the Bedlington terrier**

Copper toxicity manifests as chronic hepatitis and cirrhosis in the Bedlington terrier. An autosomal recessive mutation underlies this disease, whereby exon 2 has been deleted from the MURR1 gene (a.k.a. **COMMD1**). The MURR1 protein is a ubiquitous multi-functional protein that apparently facilitates the hepatic egress of copper into the bile. The exon 2 deletion severely truncates MURR1, and thus abrogates its ability to facilitate copper export from the liver [8].

**Cutaneous mucinosis and periodic fevers in the Shar Pei**

The Shar Pei is a breed known for its thick folded skin. Some Shar Peis exhibit cutaneous mucinosis associated with the thick folding. Hyaluronic acid is a major component of skin and hereditary cutaneous mucinosis is linked to a duplication of **HAS2** that encodes for hyaluronic acid synthetase. This duplication results in overexpression of hyaluronic acid causing the excessive folding and mucinosis, along with periodic fevers [9,10].

**Cystinuria in the Newfoundland**

Cystinuria is due to defective reabsorption of cystine in the kidney. In acidic urine, this basic amino acid will crystallize and cause obstructive calculi. In the Newfoundland, the disease is due to an autosomal recessive cystine to thymine mutation in exon 2 of the **SCL3A1** gene. This substitution leads to a nonsense mutation in a subunit of a critical dibasic amino acid transporter, thus disabling cysteine reabsorption in renal tubules [11].

**Dermoid sinus in the Rhodesian and Thai ridgeback**

In the Rhodesian ridgeback, dermoid sinus results are a consequence of an autosomal dominant mutation in which three fibroblast growth factor genes are duplicated. The duplication of the fibroblast growth factors genes leads to dysregulation of these proteins, resulting in an embryonic failure of skin and neural tube separation at the dorsal midline. An open sinus then ensues from the cervical anterior thoracic to sacrococcygeal regions [12].

**Dystrophin muscular dystrophy in the Golden Retriever**

This X-linked disease is manifested by early-onset myopathies and is due to a point mutation in intron 6 of the gene encoding dystrophin, a protein necessary for muscle function [13]. This mutation results in skipping of exon 7 and premature termination of translation of the dystrophin transcript. Dystrophin gene mutations have been characterized in other breeds and these mutations are intronic, exonic, repeat elements, or whole gene deletions [14].

**Exercise-induced collapse in Labrador Retrievers**

Exercise-induced collapse is a well-characterized autosomal recessive disorder identified in Labrador Retrievers. The disease is characterized by episodes of non-painful incoordination in the rear legs following a period of intense exercise combined with excitement or anxiety. After a period of rest, most animals return to their normal state with no evidence of collapse. The molecular basis of the disease is a single nucleotide polymorphism in exon 6 of the **DNM1** gene [15]. DNM1 encodes for dynamin 1 which is a cytoskeletal protein involved in cytokinesis and the trafficking of intracellular components [16]. The **DNM1** mutation results in an arginine for leucine substitution at amino acid 276 of dynamin 1, thus abrogating the functional activity of the protein. Dynamin 1 is needed for synaptic vesicle recycling at nerve terminals especially at times of high-frequency nerve firing. Thus the absence of dynamin 1 compromises neuronal function during the intense excitement or strenuous activity, resulting in a significant decrease in neural activity and a collapsing syndrome in affected animals. Consequently, the phenotype is mostly observed in hunting dogs, dogs used in conformational shows, or dogs used in athletic events. This phenotype is also observed in Chesapeake Bay Retrievers, Curly-coated Retrievers, Boykin Spaniels, Pembroke Welsh Corgis, and some mixed breed dogs; but other factors appear to be required for exercise-induced collapse in these breeds [15].

**Factor VII deficiency in Alaskan Klee Kai Dogs**

Factor VII deficiency is an autosomal recessive disorder identified in Alaskan Klee Kai dogs. The disease is characterized by clinically severe coagulopathy with a prolonged prothrombin time, while other clotting times are normal. Factor VII activity is reduced approximately 20-fold in these dogs. The molecular basis of the disease is a single nucleotide polymorphism (G to A substitution) in exon 5 of the gene encoding **Factor VII**. The mutation results in glycine for glutamate substitution at amino acid 96 of Factor VII, thus putatively abrogating the protease activity of the protein. A milder form of the disease has been observed in Beagles bearing the same mutation [17].

**Glucoma in Beagles**

Glucoma, the most frequent blinding disease in dogs, is characterized by increase of intraocular pressure causing retinal and optic nerve damage. Approximately 1% of Beagles exhibit primary open angle glaucoma, an autosomal recessive disorder. In these Beagles, the **ADAMST10** gene contains a mutation encoding for a Gly661Arg substitution in the myocilin protein. Myocilin is expressed in high amounts in the trabecular meshwork and myocilin Gly-661Arg is not secreted and accumulates in trabecular meshwork cells. Such an accumulation might interfere with trabecular meshwork function and lead to impaired outflow resistance [18].

**Glycogen storage disease type II (Pompe disease) in Lapphunds**

Swedish and Finnish Lapphunds are at greater risk for glycogen storage disease type II, which is also known as Pompe disease in...
humans. In this lysosomal storage disease, glycogen accumulates in vacuoles present in cells of the cerebral cortex, liver, myocardium, and smooth muscle of the esophagus. Consequently, affected dogs display progressive muscular weakness, unthriftiness, myocardial hypertrophy, and esophageal dilation-induced vomiting that typically leads to euthanasia by 18 months of age. The genetic basis for this autosomal recessive disease is a guanine to adenine substitution in the coding region of the gene encoding for acid α-glucosidase (GAA), resulting in a premature stop codon and a truncation in the enzyme. This enzyme is responsible for the conversion of glycogen to glucose in lysosomes, and the resulting truncated enzyme is unable to perform glycogenolysis and thus glycogen deleteriously accumulates in lysosomes [19].

Hemolytic anemia in the West Highland white terriers

An insertion in the pyruvate kinase gene defines the hereditary hemolytic anemia in the West Highland white terrier. In this autosomal recessive disease, the insertion of the 6 bps leads to the addition of two amino acids that perturb the function of pyruvate kinase in erythrocytes. Pyruvate kinase-deficient erythrocytes are metabolically dysfunctional and die, thus causing a regenerative anemia culminating in death by five years of age [20].

Hemophilia B in the Rhodesian ridgeback

Hemophilia B presents as mild to severe bleeding with hematomas, epistaxis, myo-hemorrhage, and joint hemorrhage. In the Rhodesian ridgeback, the disease is sex-linked (X chromosome) and caused by a guanine to adenine mutation in exon 7 of the Factor IX gene (CFIX). This SNP abrogates the function of Factor IX by introducing a glycine for a glutamate residue in the catalytic domain of this protein, which is needed for the activation of Factor X [21].

Lens luxation in the Miniature Bull terrier, Lancashire Heeler, and Jack Russell terrier

Primary lens luxation has been observed in the Bull Terrier, Lancashire Heeler, and Jack Russell Terrier. In these breeds, there is an autosomal recessive mutation involving a guanine to adenine substitution in the 5’ end of intron 10 of the ADAMST17 gene. This results in a skipping of exon 10 and a truncation of the ADAMST17 protein. The truncation of this protein leads to blindness when the lens is luxated as a result of lens zonules rupture. The varying onset of the disease suggests that some epigenetic factors are involved [22].

Leukocyte adhesion deficiency in Irish Red and White Setters

Leukocyte adhesion deficiency is an autosomal recessive disease manifested by increased susceptibility to life-threatening infectious diseases, specifically exhibited by omphalophlebitis, gingivitis, severe leukocytosis, and poor wound healing [23]. In a European study, 21% of Irish Setters were heterozygous for a guanine to cytosine substitution at nucleotide 107 of the ITGB2 gene. This mutation encodes for a Cys36Ser substitution in the glycoprotein beta-2 integrin (CD18) protein. CD18 Cys36Ser is conformationally defective, thus abrogating its ability to complex with CD11 and promote neutrophil adhesion to the vascular endothelium. The lack of adhesion leads to the immunologic dysfunction observed in certain Irish Setters [24].

Mucopolysaccharidosis in the Brazilian Terrier

Mucopolysaccharidosis is another lysosomal storage disease. In the Brazilian Terrier, this autosomal recessive condition is causally linked to a cytosine to thymine mutation in exon 5 of the gene encoding glucuronidase-β. The mutation results in a Pro⇒Leu mutation at amino acid 289 of the glucuronidase-β protein. Proline residues are integral components of protein turns, and thus the lack of this residue results in a conformational change that diminished enzymatic activity. The disease manifests as a skeletal disorder characterized by brachycephalia, dwarfism, and leg deformations [25].

Mucopolysaccharidosis type VI in the Miniature Poodle

In the Miniature Poodle, mucopolysaccharidosis is due to a 22bp deletion in the arylsulfatase B gene. As with the mucopolysaccharidosis identified in the Brazilian Terrier, this disease is autosomal recessive and leads to skeletal deformities. This deletion in the arylsulfatase B gene leads to a premature stop codon and a truncation in the enzyme, ultimately resulting in glycosaminoglycan accumulation in fibroblasts [26].

Myotonia congenita in Miniature Schnauzers

Myotonia congenita is an autosomal recessive neuromuscular disease in which dogs exhibit dental abnormalities, dysphagia, and superior prognathism, gait anomalies such as bunny hopping when running, stiff walking gait, and difficulty arising after rest [27]. The disease is associated with a thymidine to cytosine substitution in the CIC-1 gene encoding for a Met⇒Thr substitution in the D5 transmembrane segment of a voltage-gated chloride channel. The mutation prevents opening of the channel in response to the appropriate voltage [28].

Neonatal ataxia in the Coton du Tulear

A dysfunctional G protein-coupled receptor is the basis for neonatal ataxia (aka Bandera’s neonatal ataxia) in the Coton du Tulear. In this autosomal recessive disease, affected dogs have a 62bp adenine-rich retrotransposon inserted into exon 8 of GRM1 that encodes for a metabotropic glutamate receptor. The aberrant GRM1 leads to non-progressive intention tremors, head nodding, uncoordination, recumbency, and vertical ocular tremors [29].

Neonatal cerebellar cortical degeneration in Beagles

Neonatal cerebellar cortical degeneration in Beagles is associated with an autosomal recessive 8bp deletion in the coding region of SPTBN2 that encodes for β-III spectrin. This mutation leads to diminished levels of the protein resulting in Purkinje cell loss that manifests with gait abnormalities [30].

Nephropathies in the English Cocker Spaniel and Samoyed

COL4A4 encodes for alpha 4 chain of type 4 collagen, and, in a subpopulation of English Cocker Spaniels, this gene contains a single nucleotide polymorphism in exon 3 that leads to a premature stop codon in COL4A4 [31]. This autosomal recessive mutation negatively impacts basement membranes in the kidney, resulting in aberrant glomerular filtration. A similar type of mutation accounts for nephropathies in the Samoyed, where by the mutation lies in COL4A5 [32].

Neuronal ceroid lipofuscinoses

An array of breed-specific mutations underlie neuronal
lipofuscinoses in the ataxic (both static and dynamic) dog. Breeds in which a mutation has been identified include the American Staffordshire terrier, Bulldog, Dachshund, English setter, and the Tibetan terrier. Most mutations involve genes encoding either the cathepsin D or arylsulfatase proteins [33,34].

**Polycystic kidney disease in Bull Terriers**

Bull Terriers are predisposed to polycystic kidney disease in which multiple bilateral macroscopic renal cysts develop at any age, resulting in chronic renal failure in which the onset is dictated by the age of cyst development. The disease is autosomal dominant with incomplete penetrance, and is linked to a guanine to adenine substitution in the PKD1 gene encoding for a multi-domain/multi-functional protein designated as polycystin-1. The mutation leads to a glutamate for lysine substitution at amino acid 3258, in a region of the polycystin-1 with an unknown function [36].

**Renal dysplasia in the Lhasa Apso**

In a rare instance not involving a coding region of a gene, renal dysplasia in the Lhasa Apso is a autosomal dominant trait (with incomplete penetrance) involving the S’ regulatory region of a gene. The gene involved encodes for cyclooxygenase-2, a homeostatic enzyme involved in the production of eicosanoids that regulate renal function. The mutation involves small insertions and deletions of a GC-rich region upstream of the SP11 transcription factor-binding site, resulting in diminished expression of cyclooxygenase-2. Affected dogs have immature glomeruli, mineralized tubules, and diffuse interstitial fibrosis [36].

**Retinal atrophy in the Cardigan Welsh corgi and Irish setter**

Retinal atrophy in the Cardigan Welsh Corgi is associated with an autosomal recessive 1bp deletion in intron 18 of PDE6A gene. PDE6A encodes for the alpha subunit of cGMP phosphodiesterase, and the frame shift mutation leads to a premature stop codon in the middle of the catalytic portion of the enzyme [37]. In the Irish setter, the disease is due to a nonsense amber mutation (premature stop codon) in exon 21 of PDE6B which encodes the beta subunit of the same enzyme. This 49 amino acid truncation eliminates carboxyl-terminal residues needed to membrane association. The functional absence of this enzyme leads to rod-cone dysplasia, manifested by early-onset clinical signs [38].

**Retinal dystrophy in Schapendoes**

This type of retinal atrophy begins as night blindness and progresses to complete vision loss. Mydriasis and a change in tapetal reflectivity are also observed in this disease. This is an autosomal recessive condition involving a 1bp insertion in exon 6 of CCDC66, resulting in a premature stop codon that truncates a protein designated as coiled coil domain containing 66 [39].

**Retinal atrophy in the Sloughi**

Retinal atrophy in the Sloughi is analogous to that observed in the Cardigan Welsh Corgi. The only difference is the Sloughi-specific mutation is an 8bp insertion in exon 8 of the PDE6B gene, whereas the mutation is found in the PDE6A gene in the Cardigan Welsh Corgi [40].
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<td>N/A</td>
<td>(Docampo et al. 2000; Otisso et al. 2011)</td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
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<td>Nephropathy</td>
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</table>

Table 1: Summary of 36 breed-associated canine diseases with a single gene mutation underlying each condition. N/A: None available at this time.
Beagles were the only breed represented more than once in this group of diseases. This is not surprisingly since this breed is often used a research model. Also not surprising was our findings that most (80%) of the 36 diseases are autosomal recessive. It is of note that nucleotide substitutions were the most common (42%), followed by deletions (28%), insertions (14%), and duplications (10%).

The majority (91%) of the mutations involve coding regions, resulting in amino acid substitutions or truncations in the encoded protein. The other 9% involved intronic or 5’ regulatory region mutations. Interestingly, none of the mutations introduced a high-affinity RNAi site like that observed in single nucleotide mutations. Interestingly, none of the mutations introduced a high-affinity RNAi site like that observed in single nucleotide polymorphisms found in catle [49] and sheep [50].

In summary, this review encapsulates a representative set of canine pathologies associated with single genetic defects. Most of these diseases are autosomal recessive substitutions in the coding regions of genes encoding proteins involved in the neurologic and visual systems. Genetic tests are available for most of the conditions.

References


