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FROM THE EDITOR . . .

I hope you all are enjoying your summer. We’re happy to be back to publishing Wheaten HealthNews after a hiatus to help with the rollout of the PLN Variant Gene Test last year! When you’re planning your summer activities, don’t forget to include plenty of water for your dogs; and never leave your dog in the car in warm weather, not even for a few minutes! For some great tips on coping with fireworks and those summer thunderstorms, check out Dr. Phil Zeltzman’s article in this issue. Dr. Zelztman’s tips also include a link to a video done by a vet that shows “What it’s like to be a dog left in a hot car”. The video is very informative and should be shared with new puppy owners. While on the subject of websites, Penn Vet has launched a new website at www.vet.upenn.edu. Visit it often for interesting developments in canine health care.

We have included articles on the PLN Variant Gene Test that are also in the current issue of Benchmarks. They are well worth a second read if you saw them in Benchmarks; and if not, please enjoy them in this issue. An excellent article on Canine Hip Evaluations and Hip Dysplasia is part of this issue along with our thanks to Dog Fancy for their permission to reprint. We receive lots of questions on vaccinations, and Dr. Jean Dodds’s current Vaccine Protocol is included in this issue. Of course, as she notes, talk with your vet about the protocol appropriate for your dog.

We are debuting a new column called “The Heart of the Matter” where we will feature owner accounts of how they dealt with their dog’s particular health issue. We hope these stories will be both informative and inspirational. If you have a story you’d like to share, please contact us. All areas of health are of interest and are welcome!!!

Have fun and stay cool!

For the love of the dogs…,
—Cecily Skinner
UPDATE ON DNA MARKER TESTING

— DNA TEST LIABILITY PAM MANDEVILLE AND THE SCWTCA HEALTH COMMITTEE.

INFORMATION TO OWNERS/BREEDERS

We are working on articles that will be available on the website as references:
- DNA for the Befuddled: A “plain language” article on some terms and concepts we’re all encountering now; and
- An Owner’s Guide to the Test: An article directed to owners and potential owners to understand the meaning of results as they relate to a pet dog.

As a result of a few questions I’ve received, I asked Robyn to clarify on the website that kits are available from U0fpenn and how owners living outside the United States can obtain kits. These reminders were posted on the various discussion listservs.

JUNE 2013 BENCHMARKS

This issue represents a year since the test was introduced. We proposed to the editor that we highlight where we are later, and we appreciate her cooperation.

Dr. Littman provided an updated article on her research [see p.8 of this issue], which included a report on the 1200+ samples that she received — in large measure — due to the efforts of the test kit team and SCWTA, the GRF, and the Endowment last year. This table, from her article, shows the variant allele frequency by country:

<table>
<thead>
<tr>
<th>Country</th>
<th>1-1</th>
<th>1-2</th>
<th>2-2</th>
<th>Variant Allele Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA, n=880 (Hardy-Weinberg expected frequencies in the USA)</td>
<td>33</td>
<td>48</td>
<td>19</td>
<td>43 (32.5) (49) (18.5)</td>
</tr>
<tr>
<td>Canada, n=108</td>
<td>40</td>
<td>52</td>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td>Total USA and Canada, n=988</td>
<td>34</td>
<td>48</td>
<td>18</td>
<td>42</td>
</tr>
<tr>
<td>Nordic Countries, n=93</td>
<td>43</td>
<td>41</td>
<td>16</td>
<td>37</td>
</tr>
<tr>
<td>UK/Ireland, n=100</td>
<td>65</td>
<td>23</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Other countries (Australia, Poland, Argentina), n=27</td>
<td>63</td>
<td>30</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>Total all countries, n=1208 (Unknown Sex, n=11)</td>
<td>38</td>
<td>45</td>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>Females, n=712</td>
<td>38</td>
<td>45</td>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>Males, n=485</td>
<td>38</td>
<td>44</td>
<td>18</td>
<td>40</td>
</tr>
</tbody>
</table>

Note that the headers represent the following:
- 1-1 – Homozygous negative (0 copies of the variant markers),
- 1-2 – Heterozygous (1 copy of the variant markers), and
- 2-2 – Homozygous positive (2 copies of the variant markers).

SCWTCA Member Neil O’Sullivan also provided an article “What Does Gene Testing Mean?” This piece is a brief summary, in more “lay” terms, of Drs. Littman and Henthorn’s journal article; but its real focus is on how breeders use the results and what they mean. The combination of Neil’s professional background as a geneticist and personal experience as a breeder give his observations particular value, and his contribution is very much appreciated.

While SCWTCA members may approach the use of this test in different ways, it appears that most have incorporated it into their breeding practices. We feel that’s the mark of a successful first year.
STUDENT RESEARCHER REPORT

—CLAIRE WILEY, PENN VET CLASS 2013

Last May, I had a life-changing experience at the 6th international conference on “Advances in Canine and Feline Genomics and Inherited Diseases” in Visby, Sweden. The conference was held in a medieval city, which was a beautiful backdrop of castles and ruins. While there I gave a fifteen-minute presentation entitled “Protein-Losing Nephropathy and Mutations in NPHS1 and KIRREL2 in Soft-Coated Wheaten Terriers.” This presentation shared a genetic component of PLN identified in Wheatens, a breakthrough that is the culmination of work by Drs. Meryl Littman and Paula Henthorn, SCWTCA, and numerous Wheaten breeders and owners. I also received a student award for our abstract.

As I stood at the podium about to speak the first words of my presentation, I tried to avoid scanning the crowd for familiar faces. Pioneers of canine and feline genomics from across the globe were at attention to hear my small contribution to their field. For an instant my eyes met those of Kerstin Lindblad-Toh, a Swedish scientist who led the effort to sequence and analyze genomes of not only the dog, but the horse, chimpanzee, mouse, and opossum as well. I averted my gaze quickly, but my stomach churned even more as I heard Elaine Ostrander cough over video conference. The renowned researcher was unable to attend due to a recent injury, but earlier that day she presented her work via Skype on identifying genes [that are] the genetic basis of the varying shapes of dog skulls. She already discovered genes responsible for the vast size disparity in dogs, from toy poodles to Irish wolfhounds. Although I gave a similar presentation for a research day at Penn Vet, I had never before presented anything to a large group of knowledgeable scientists at the forefront of their field. I then spotted my mentor, Paula Henthorn, who gave me an encouraging smile. With a deep sigh, I quelled my awe and fear and plunged into the story of Wheatens and PLN.

That night the conference hosted a medieval dinner at an 11th century castle. I dined with a PhD student from Liverpool, who specializes in the computer programs we use to analyze DNA. He offered his assistance with future projects as we drank meade and watched jesters swallow flames. Later I caught up with a colleague who had returned to her home in Turkey after completing a project at Penn Vet. The night became morning as I had lively conversations with scientists, veterinarians, and students from France, Spain, Turkey, Sweden, and Israel.

Attending this conference was invaluable to furthering my veterinary career and widening my cultural horizons. My participation would not have been possible without the generous contribution from the SCWTCA Endowment Grant.

Biographic Information

Claire Wiley is a senior veterinary student at the University of Pennsylvania. During the summers of 2011-12, Claire worked with Dr. Paula Henthorn and Dr. Meryl Littman while they developed the DNA test we are using to make better breeding decisions. Subsequently, Claire traveled to Visby, Sweden in the summer of 2012, partially funded by the SCWTA Endowment Student Researcher Award, to present the material described above. She coauthored the seminal publication: Littman MP, Wiley CA, Raducha MG, Henthorn PS. Glomerulopathy and mutations in NPHS1 and KIRREL2 in Soft Coated Wheaten Terrier Dogs. Mamm Genome 2013;24:119-126. Graduating from Penn Vet in May, Claire and her twin sister Lauren, matched successfully to pursue their internships at Penn Vet, starting in July 2013. Hopefully, SCWCTA will have further dealings with Claire and Lauren!
 Thirty years ago this December, I met my first Wheaten at the Veterinary Hospital of the University of Pennsylvania. Her owners were breeders and knew of other sick Wheatens. Before long I was getting medical records concerning sick Wheatens from all over North America. I could see that Wheatens were predisposed to a number of diseases and that different dogs were actually ill with a variety of diseases, sometimes in combinations, including: protein-losing nephropathy (PLN), inflammatory bowel disease (IBD, often involving food allergies), protein-losing enteropathy (PLE) due to IBD and/or intestinal lymphangiectasia, Addison’s disease, and juvenile renal disease (JRD, aka renal dysplasia). People confused these diseases with one another because of similar clinical signs and some similar abnormal blood and urine test results. We started banking DNA samples from sick dogs and geriatric dogs with well-characterized phenotypes, and started the SCWT Open Registry to help stop rumors about which dog had which disease, to see if familial relationships might detect possible modes of inheritance, and to help educate people as to the prevalence of these health problems. In the 2011 update of the Open Registry, more than 1100 dogs are listed, showing that PLN is the biggest problem in the breed; 722 dogs had PLN (279 of these had PLE/PLN combined), another 222 had IBD or PLE alone, 98 had Addison’s disease, and 66 had JRD. We found there was no age limit for PLE and/or PLN, no predictive tests; and inheritance appeared complex, probably involving multiple genes, variable expression, incomplete penetrance, and possibly environmental triggers.

Technology finally came of age to use our banked DNA samples in a genome-wide association study, which honed our attention to a statistically significant area of the genome that was different in affected dogs. Fine mapping of candidate genes in this area showed variant alleles in 2 genes (NPHS1 and KIRREL2) which are next to each other on the same chromosome and in complete linkage disequilibrium (i.e., variations are almost always linked together) that encode 2 slit diaphragm proteins in the glomerulus of the kidney (nephrin and filtrim/NEPH3). The variant alleles are SNPs (single nucleotide polymorphisms), one in each gene, which cause a change in one amino acid in each of the proteins they encode, causing a structural abnormality and functional permeability defect allowing for protein loss into the urine. These abnormal glomeruli may be more likely to leak if additional glomerular damage occurs. This is the first podocytopathy discovered in dogs and is a model for inherited PLN in people. In fact, there are at least 176 different variant alleles found in NPHS1 (nephrin) that have been described in people with PLN.

Our retrospective studies showed that dogs homozygous positive for the variant alleles were at highest risk for developing PLN, heterozygous dogs were at intermediate risk, and homozygous negative dogs were at very low risk. It may be that homozygous positive or heterozygous dogs are triggered to get PLN if they have allergies, IBD, PLE, Addison’s, or other inflammatory or immune-mediated diseases, because theoretically their abnormal glomeruli may not be able to handle the added wear and tear of immune complexes passively deposited in the glomeruli. Many future studies are proposed as we look at dogs with known genotypes prospectively and follow them throughout their lives.
The DNA test for the PLN-associated variant alleles is now available for Wheatens (and Airedales; among 114 breeds tested, only SCWT and Airedales had these variations, aka mutations). By testing dogs, we can know their individual risk for PLN as well as choose a mate to try to avoid producing puppies with high risk of developing PLN. The test does not tell which dogs should be bred, but it does help with deciding which dog to breed to.

We need to be very careful NOT to cull all carriers since that will cause loss of genetic diversity in the breed which can lead to other genetic problems revealing themselves. We need to avoid using a small foundation stock, popular sires, or inbreeding. This test is just another tool to use in decision making, to be considered along with other important characteristics such as temperament, other health predispositions for which there are no genetic tests yet (e.g., allergies, PLE, Addison’s disease), conformation, etc. So far, results show that roughly 1/2 the submissions are heterozygous, 1/3 are clear, and 1/6 are homozygous positive. If only the clear dogs were used in breeding, we would lose 2/3 of the population (!); and considering that only ¼ of the remaining dogs are males, and some of them would be culled for poor temperament, poor conformation, severe allergies, IBD/PLE, etc, we fear that we would be left with popular sire effects and inbreeding, which would lead again to bottlenecks and new and maybe worse genetic problems. Realize that PLN, when picked up early, may be treatable for many years. Knowing that a dog is at high risk should increase monitoring and recognition of whether a dog is starting to show signs of PLN warranting intervention.


One problem we have noticed is that people may be using terminology on their own that will be confusing when compared with geneticist’s terminology. We have seen some breeders use a zero (“0”) in place for a wild-type (normal) allele, and a “1” for the variant (mutated) allele. That is NOT the abbreviation used by geneticists. Zeros are only used for an unknown result. A “1” is used to denote the normal allele and a “2” is used to denote the variant allele. Thus, a “1-1” in OUR system is a clear (homozygous negative) genotype, a “1-2” denotes a heterozygous genotype, and a “2-2” is a homozygous positive genotype.

We have received many DNA samples for a prevalence study conducted May-Oct 2012. Below is an abstract of our findings from the first 1208 submissions, which will be published in the *Journal of Veterinary Internal Medicine* in April, 2013 and will be presented as a poster at the ACVIM Forum in Seattle in June.

I wish to thank everyone who participated in the seroprevalence study and all the owners, breeders, students and veterinarians who helped over these past 30 years, sending in information and samples. I especially want to thank our geneticist, Paula Henthorn! We have found a big piece of the PLN puzzle; but more studies are needed to follow dogs prospectively, now that we know their genotypes, to know what the risk is for them to develop PLN during their lifetimes. We want to know if there are more genes involved that put dogs at risk for PLN or that appear to protect them. Moving forward, studies are needed to understand and detect genetic variations leading to risk for PLE, IBD, allergies, Addison’s disease, and JRD. Please continue to support researchers interested in all these problems, at Penn and elsewhere. The Wheaten community is amazingly supportive, and I’m glad that my career path just happened to lead me to you. Thanks again for all your support.
PREVALENCE OF VARIANT ALLELES ASSOCIATED WITH PROTEIN-LOSING NEPHROPATHY IN SOFT COATED WHEATEN TERRIERS

MP LITTMAN, MG RADUCHA, PS HENTHORN. UNIVERSITY OF PENNSYLVANIA SCHOOL OF VETERINARY MEDICINE, PHILADELPHIA, PA.

Variant alleles in NPSH1 and KIRREL2, the genes which encode the slit diaphragm proteins nephrin and filtrim/Neph3, respectively, were previously found associated with protein-losing nephropathy (PLN) in Soft Coated Wheaten Terriers (SCWT) by a genome-wide association study and subsequent gene sequencing of candidate genes in a statistically significant interval that differed among dogs with PLN compared with geriatric (14-18 year old) SCWT. Genotyping assays were developed for both of the single nucleotide polymorphisms (SNPs) in these genes that are in linkage disequilibrium in the breed. Homozygous positive dogs were shown to be at highest risk for the development of PLN, heterozygous dogs were at intermediate risk, and homozygous negative dogs were at low risk for the development of PLN. A prevalence study was performed to ascertain if breeders could safely remove carrier dogs in one generation. Cheek swab, blood, or semen samples were tested from 1208 SCWT dogs of all ages (median 4 yrs). Haplotypes are described as 1-1 (homozygous negative), 1-2 (heterozygous), and 2-2 (homozygous positive) for the PLN-associated variant alleles. The following table shows the frequencies found in various countries.

<table>
<thead>
<tr>
<th>Various Countries &amp; Areas of the Wheaten World</th>
<th>Haplotypes</th>
<th>Variant Allele Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA, n=880 (Hardy-Weinberg expected frequencies in the USA)</td>
<td>1-1 33 (32.5)</td>
<td>1-2 48 (49)</td>
</tr>
<tr>
<td>CANADA, n=108</td>
<td>40</td>
<td>52</td>
</tr>
<tr>
<td><strong>Total USA and Canada, n=988</strong></td>
<td>34</td>
<td>48</td>
</tr>
<tr>
<td>NORDIC COUNTRIES, n=93</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>UK/IRELAND, n=100</td>
<td>65</td>
<td>23</td>
</tr>
<tr>
<td>OTHER COUNTRIES (AUSTRALIA, POLAND, ARGENTINA), n=27</td>
<td>63</td>
<td>30</td>
</tr>
<tr>
<td><strong>Total all countries, n=1208 (Unknown Sex, n=11)</strong></td>
<td>38</td>
<td>45</td>
</tr>
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<td>FEMALES, n=712</td>
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<td>45</td>
</tr>
<tr>
<td>MALES, n=485</td>
<td>38</td>
<td>44</td>
</tr>
</tbody>
</table>

Without genetic counseling with the knowledge of these haplotypes and assuming random breeding, the variant allele frequency would remain 43% in the USA. This high frequency indicates that it would be unwise to cull all carriers (1-2 or 2-2 dogs) of the variant alleles in one generation, thereby risking loss of genetic diversity, increased inbreeding, and the potential of increasing the incidence of other deleterious genetic traits. An approach to avoid producing high risk homozygous positive (2-2) dogs would be to preferably breed desirable heterozygous (1-2) or homozygous positive (2-2) dogs to homozygous negative (1-1) dogs.
COMMENTS ON DR. LITTMAN’S LETTER

Dr. Littman’s long-term efforts researching PLN in Wheatens has produced many benefits to Wheatens affected with PLN: improving diagnosis, treatment, and quality of life for our Wheatens with the disease (Littman, 2011). Her work has helped breeders and clinical practitioners alike, to better understand this disease. Her recently published, groundbreaking research in collaboration with Dr. Henthorn now allows us to test for and better understand the basic biology of the disease, including its most common form which has an underlying genetic basis (Littman et al., 2013).

Their work developed from the painstakingly detailed work that was carried out over decades. It amassed many hundreds of samples from Wheatens affected with PLN, including their in-depth medical histories and pedigrees. In addition, she also gathered geriatric ‘normal’ dogs, documented equally painstakingly with their medical histories and pedigrees in the samples. The first part of her work is published and updated in the Open Registry and made available to members of the Open Registry. This huge body of work then allowed the researchers to scan the DNA of both affected and normal dogs with a SNP chip to see if patterns within the DNA showed affected and normal dogs differing at one or more regions of the DNA. This detailed genetic work is very commonplace today, but within the dog world, less commonly found because of the rigorous background work needed to build such a database. Dr. Littman and her team achieved this with the Wheatens by screening them for both the Open Registry and the geriatric normal studies. This quality of database is not common among dog breeds.

This scan of the Wheaten DNA found that the normal and affected dogs differed in their DNA sequences for two genes involved in building the structures that help with filtration in the kidneys. These two genes, each with a mutated allele, were very closely linked on the same chromosome, and so inherited as a single unit. This close linkage of two genes on a chromosome is referred to as a haplotype. All dogs studied in the initial study have shown no breakup in the linkage, so we would state that there are two common haplotypes documented in Wheatens. One dog has now been identified which is the result of a crossover between the two common haplotypes. So one rare haplotype has now also been identified. So far, either the normal alleles for both genes are inherited together (as one of the two common haplotype) or both mutated alleles are inherited together (as the other common haplotype). Of 105 breeds tested, these mutations are known only to occur in Wheaten Terriers, with the exception of two Airedale Terriers — one of whom was homozygous for the mutation and was affected with PLN, and one bloodhound.

In their work, because the samples sizes were so large, the researchers were able to extensively survey Wheatens and calculate the Odds Ratio (OR). We now know that having two copies (being homozygous) for the alleles with the mutations mean those Wheatens are at a very high risk of developing PLN. These dogs are homozygous (2-2) for the markers. Dogs with one copy of
the mutation marker and one normal marker (1-2) are heterozygous dogs, at a lower risk of developing PLN compared to the homozygous (2-2) dogs. The dogs at least risk of developing PLN are the homozygous (1-1) dogs. While almost all cases of PLN in Wheatens were due to mutations in these two genes, a very small number of Wheatens were found with other risk factors such as Amyloidosis. This disease can cause PLN, independent from the genetic mutations commonly found to cause PLN in Wheatens.

So how do breeders use this new tool? Most breeders will want to breed using a technique known as marker assisted selection. Parents (or grandparents) of possible breedings can be screened with the new test.

Dogs which are 1-1 can be freely intermated with the PLN risk reduced to a minuscule level. Breeding decisions among 1-1 dogs will involve all the other criteria that need to be considered but with PLN no longer a factor in the decision process.

Dogs with 1-2 markers can be bred to 1-1 dogs; and only the resulting 1-2 dogs will have any significant risk of developing PLN. However, since we now know that more Wheatens are likely to carry the mutation (76% of the geriatric normals were carriers of one or two copies of the allele) then a mating of a 1-2 to 1-1 will be an improvement as only 50% of the progeny carry a single copy of the marker and 50% are clear (1-1). This mating produces no progeny in the highest risk group of 2-2 which carries the highest risk of developing PLN. Remember: in all 145 Wheatens studied, only 11% were 1-1 in genotype; and among the geriatric normals (an elite group for status with respect to this disease), only 24% were 1-1. Since the release of the test, we see in the results that the Wheaten population actually looks more like the geriatric normal population for mutation frequency than the combined affected dogs and geriatric normal dogs used for the initial screenings. So a 1-2 to a 1-1 mating is helping to improve the population and greatly reduce the frequency of PLN cases.

A 2-2 to 1-1 breeding produces all puppies who are 1-2. This is the average status of the breed currently (roughly 50% of all Wheatens tested are 1-2) and isn't a step backwards. It is a status quo mating.

A 2-2 to 1-1 mating will result in 50% 2-2 puppies at high risk of PLN and 50% 1-2 puppies at moderate risk of PLN. This mating is increasing the frequency of the disease-causing alleles and therefore should be a breeding that is discouraged. Doing such a mating will increase the risk of more PLN cases compared to the average population of Wheatens currently tested.

A 1-2 to 1-2 mating will result in 25% 2-2 puppies, 50% 1-2 puppies, and 25% 1-1 puppies. This also is a status quo mating as it doesn't improve the population by lowering the risk of PLN compared to our current status. Since it produces 25% 2-2 puppies at highest risk of being affected by PLN, this mating should also be discouraged.

In future years, as the frequency of the mutated alleles decreases with the power of marker assisted selection; and as people take advantage of 1-1 Wheatens of quality in the population, the frequency of PLN cases will drop to very low levels in the SCWT. The screening of parents prior to evaluation of breeding stock and screening and selection of 1-1 puppies among litters where the options are between 1-1 and 1-2 status puppies will increase the frequency of normal alleles in the population. It would be recommended to avoid 2-2 for future breeding candidates so that we see PLN fade to the status of a rare disease in the SCWT population. Breeders should screen their current stock and develop a plan for their breeding program to have a long-term goal of 1-1 stock. However, depending on each breeder’s current starting point, this goal may take three or more generations to achieve.

Wheaten breeders need to use this test wisely; rushing to the small pool of 1-1 Wheatens currently available in the gene pool would reduce the genetic variation in the Wheaten
population and create a bottleneck which would have unpredictable but negative results for the future. Are there dogs of 2-2 status who should be bred currently? Of course there are. They are elite individuals who offer much-needed genetic diversity to the SCWT gene pool. However, programs should be developed to achieve no disease-causing alleles for PLN in future generations. All the other normal healthy genes from these 2-2 dogs will be maintained through wise breeding. This test provides the opportunity for a brighter future for the SCWT. It should be used widely. Breeders must remember it is a screening tool, to be utilized over many generations, with the goal of having a breed at a very low risk of PLN, making Wheatens similar to other breeds of dogs screened in Dr Littman’s studies found to be at low PLN risk.

REFERENCES


GLOSSARY OF TERMS AS USED IN DR. O’SULLIVAN’S ARTICLE

Allele — is an alternative form of a gene; for example, white vs. brown allele in color gene.

Gene — is a segment of DNA in a specific location on a chromosome that details the blueprint for a protein.

Gene Pool — is the collective of all genes, with their alternate alleles, in a population. A large gene pool reflects extensive genetic diversity, making such populations robust with high fitness and able to resist bouts of intensive selection.

Genotyping — is a DNA screening process allowing the alleles that an individual has inherited from its parents to be accurately determined by biological assays.

Haplotype — is a combination of genes or markers that are closely linked on the same chromosome and are inherited usually as a block. Rare crossovers, breaking up these linkages, can occur and result in the reaction of a new Haplotype.

Homozygous — is an individual gene that has two copies of the same allele.

Heterozygous — is an individual gene that has both copies of the different alleles.

Linked genes — every chromosome is made up of many genes, like beads on a string; linked genes are on the same chromosome, so are normally inherited together as a single block.

MAS (marker assisted selection) — is the selection of animals using additional information on a limited number of markers associated with traits of interest.

Mutation — is a process that changes the sequence of a gene and, therefore, giving rise to a new allele which changes the form produced by the new mutated allele. Most mutations are neutral; only a tiny percentage of these changes result in improved or deteriorated gene performance.

Odds Ratio (OR) — the odds ratio is the relative odds of an event happening in one group when compared to the odds that the event occurs in another group.

SNP (single nucleotide polymorphism) — is a change in a DNA molecule at a single position. For example, ATTGCT->ATCGCT (the second T changes to a C) which creates two alternative alleles.

SNP chip (or microarray) — is the technology that allows rapid and relatively inexpensive simultaneous genotyping at many positions in the genome.
Prevalence of Variant Alleles Associated with Protein-Losing Nephropathy in Soft Coated Wheaten Terriers

Meryl P. Litman*, Michael G. Raducha and Paula S. Henthornton, University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA

Abstract

Variant alleles in NPHS1 and KIRREL2, the genes which encode the slit diaphragm proteins nephrin and fritin/Neph1, respectively, were previously found associated with protein-losing nephropathy (PLN) in Soft Coated wheaten terriers (SCTWT) by a genome-wide association study and subsequent gene sequencing of candidate genes in a statistically significant interval that differed among dogs with PLN compared with geriatric (14-18 year old) SCTWT. Genotyping assays were developed for both of the single nucleotide polymorphisms (SNPs) in these genes that are in linkage disequilibrium in the breed. Homozygous positive dogs were shown to be at highest risk for the development of PLN, heterozygous dogs were at intermediate risk, and homzygous negative dogs were at low risk for the development of PLN. A prevalence study was performed to ascertain if breeders could safely remove carrier dogs in one generation. Check swabs, blood, or semen samples were tested from 1208 SCTWT dogs of all ages (median 4 yrs). Haplotypes are described as 1-1 (homozygous negative), 1-2 (heterozygous), and 2-2 (homozygous positive) for the PLN associated variants. The following table shows the frequencies found in various countries.

<table>
<thead>
<tr>
<th>Country</th>
<th>USA</th>
<th>Canada</th>
<th>Nordic, + Ireland</th>
<th>Other, Poland, Argentina</th>
<th>Total all, n=1208</th>
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<td>38</td>
<td>44</td>
<td>40</td>
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</tr>
</tbody>
</table>

Without genetic counseling with the knowledge of these haplotypes and assuming random breeding, the variant allele frequency would remain 43% in the USA. This high frequency indicates that it would be difficult to impossible to eliminate carriers (1-2-2 dogs) of the variant alleles in one generation, thereby risking loss of genetic diversity, increased inbreeding, and the potential of increasing the incidence of other ditributive genetic traits. An approach to avoid producing high-risk homozygous positive (2-2) dogs would be to preferably breed desirable heterozygous (1-2) or homzygous positive (2-2) dogs to homzygous negative (1-1) dogs.

Background

- The SCTWT breed is predisposed to having PLN and 5-15% appear to be affected.
- There are 722 PLN dogs listed as being affected on the SCWT Open Registry.
- Great is 10-13 yrs old and there is no age limit and no early biomarkers exist.
- The mode of inheritance appears complex with multiple genes and environmental triggers.
- Proteinuria may be accompanied by hypertension, hemorrhage, thrombocytopenia, edema, febrile events, edema/puffiness, and subcutaneous, renal, or pulmonary failure.
- A genome-wide association study compared DNA of affected dogs and 14 controls.
- A significant difference of Inclusion for PLN cases was found on chromosome 1 (Fig. 1). The term 3% confidence interval comprised 45 dogs, including genes possibly related to PLN.
- Sequencing of the candidate genes found nonsynonymous single nucleotide polymorphisms (SNPs) in 2 genes which encode 2 slit diaphragm glomerular protein.
- NPHS1 (nephrin): 6 – G to A in 6 conserves 6; changed glycine – Arginine
- KIRREL2 (fritin/Neph1, one of the NEPH1 proteins): C > G; changed Proline → Arginine in a conserved Proline-rich interval (Fig. 2).
- The variance allele is in linkage disequilibrium with other variants.
- Of 747 dogs of 114 other breeds, only 3 dogs (Airédale, Bloodhound) had these SNPs. 2-2 dogs at high risk (DK=0,66%, 95% CI=4.24-19.35), 1-2 dogs at intermediate risk, 1-1 dogs are at low risk for PLN (Fisher's exact test, 2 x 2 contingency table, 2-tailed = 7.78 x 10^-9)

Prevalence Study

- Custom TaqMan genotyping assays (Illumina) were developed for each of these SNPs.
- The DNA test for PLN associated variant alleles is available at Penn Vet since May 2012.
- Pedigrees were compared to DNA samples from 900 dogs in the Open Registry.
- Phenotypic and genotypic information was analyzed.
- The DNA test for the variant allele was developed in NPHS1 and KIRREL2 by TaqMan methodology.
- The 1-1 and 2-2 alleles are highly associated with PLN.
- The 1-2 alleles were not significantly associated with PLN.
- The 1-2 allele was inherited from the parents.
- All of these dogs have been tested for the DNA test.
- Of these popular puppies, 4 were haplotype 1-1, and 1 dog haplotype 2-2.
- There was no difference in allele frequency associated with age, possibly due to the small sample size (1% of registered SCWT's tested).
- Breeding breeders are testing for these DNA tests and selecting breeding away from affected and their relatives over the years.

Conclusions

- The PLN at-risk variant alleles are common in the breed and found internationally.
- Testing individuals helps to assess their lifetime risk for developing PLN.
- Breeding stock is selected to select for those which will not produce homozygous positive puppies.
- Cutting all carriers in one or two generations would not be wise, because of risk for decreased genetic diversity, which could lead to increased inbreeding and risk for additional inherited disorders.

References


Acknowledgements

The authors thank the many veterinary centers for their support, and breeders and owners who helped with this work. Special thanks to go to Dr. Claire A. Willey. Financial support was from the Foundation for the Soft Coated Wheaten Terrier Club of America Endowment, Inc., and the American Kennel Club – Canine Health Foundation. We are indebted to current and former members of the SCWTA, SCAW, and the University of Pennsylvania School of Veterinary Medicine. The authors have no conflict of interest to report.
EXCITING NEWS FOR DR. MERYL LITTMAN!

The SCWTCA and the breeders and owners of Soft Coated Wheaten Terriers everywhere extend their congratulations to Dr. Littman on her becoming a Full Professor!

Dr. Littman has been dedicated to Wheaten health issues for many, many years. Together with Dr. Paula Henthorn, she was able to provide breeders with a valuable new tool in our efforts to eliminate PLN: the PLN Variant Gene Test, more widely known as the “DNA Test”!

This past month, Dr. Littman presented her poster on the Prevalence of Variant Alleles Associated With Protein-Losing Nephropathy in Soft Coated Wheaten Terriers at the ACVIM Conference in Seattle, WA.

We present the poster on the page opposite.

TREATMENT OF URINARY INCONTINENCE — THE AKC CHF JANUARY 2013 FEATURED GRANT:

Dr. Shelly Vaden at North Carolina State University is examining the usefulness of cultured muscle cells for the restoration of function of the urethral sphincter in dogs with naturally occurring urinary incontinence.
The Role of Oxidative Stress in IMHA

01/15/2013

Immune-mediated hemolytic anemia (IMHA) is a major cause of severe anemia in American dogs. IMHA occurs when the immune system attacks and destroys oxygen-carrying red blood cells (RBC), leading to symptoms including exhaustion, weakness, and panting. However, although scientists have known for years that the immune system destroys the RBCs in dogs with IMHA, they still have no idea what prompts it to attack. That’s why, with the help of the AKC Canine Health Foundation, researchers from the University of Guelph set out to compare the antibodies found on the RBCs of dogs with IMHA to those found on the RBCs of healthy dogs and dogs with other forms of anemia.

There are several mechanisms through which the immune system could target and destroy RBC. However, one critical element of any attack is recognition, and the immune system’s way of recognizing targets is through the production of antibodies. By analyzing what antibodies were bound to the blood cells of the three different groups of dogs, the scientists’ goal was to determine which targets were associated with premature cell destruction.

As it turns out, simply having antibodies bound to RBCs was not enough to cause IMHA. Every single dog that was tested had antibodies bound to a protein known as anion exchanger 1 (AE1). That’s not surprising, as AE1 is a protein expressed by older RBCs that are ready to be recycled by the body. It is a signal that the cells are ready to be destroyed. What the scientists needed to discover was whether dogs with IMHA also had antibodies targeting other proteins found in younger RBCs, cells that would normally have lived longer lives. They did. Dogs with IMHA also had antibodies bound to a number of other RBC proteins while healthy dogs, and dogs with other forms of anemia, did not. In addition, when their circulating antibodies were tested, the immune systems of dogs with IMHA targeted a larger number of RBC proteins than those of healthy dogs or dogs with other forms of anemia.

The telling piece of information was not that the immune systems of dogs with IMHA were on the attack. It was the specific proteins that the antibodies were latching on to. It turned out that dogs with IMHA were making antibodies against RBC proteins that are normally only “visible” in the blood during times of severe oxidative stress. That critical piece of data lent strong support to the idea that oxidative stress plays a role in the development of the disease, something that had been suggested by other studies.

It’s still too early to know whether oxidative stress leads to the development of IMHA or IMHA creates an environment where there is increased oxidative stress. However, this research is certain to prompt further investigation into such questions. It may even encourage scientists to look for other potential interactions between oxidative stress and the development of autoimmune disease, a relationship that, if found, could have a profound effect on our understanding of the nature of these increasingly common diseases.

This work was funded by AKC Canine Health Foundation grant 1013-A.

Publications:

There are over 1100 Wheaten samples stored in the DNA bank at the University of Missouri. Most were collected as part of the Canine Phenome Project (CPP) during 2009 - 2011. The CPP Health Survey has been completed by owners of 759 of the dogs.

Genetic research conducted at the University of Missouri using Wheaten DNA samples includes studies on degenerative myelopathy (on-going), an unnamed movement disorder in young Wheatens described as episodic dyskinesia/ataxia (on-going), primary lens luxation (2009), and the Wheaten sibling pairs protein-losing comparison study (2010).

As of October 2012, 77 Wheaten samples had been tested using the degenerative myelopathy DNA test developed at the University of Missouri. Of those, 43 tested normal, 14 tested carrier, and 20 tested as affected/at risk. Spinal tissue pathology confirmed DM in previously clinically diagnosed Wheatens in 2011. DM DNA test results corresponded to the pathology results. Also in 2011, DNA test results were “at risk/affected” for 11 of 12 Wheatens with clinical symptoms referred to the University. Information about DM and the DNA test is at [www.caninegeneticdiseases.net](http://www.caninegeneticdiseases.net).

Randomly selected Wheaten DNA samples were tested for the mutation that causes primary lens luxation in other breeds. All Wheaten samples were normal (no copies of the mutation). CERF statistics for 2000-2008 reported a very low incidence of lens luxation in Wheatsens (3 cases or one-tenth of one percent).

A synopsis of the Wheaten Sibling Pairs Study was included in the October 2010 and October 2011 reports in Wavelengths. Results were inconclusive.

Wheaten DNA stored at the University of Missouri will also be shared with researchers at other institutions for studies that meet specific criteria. This includes the NIH SCWT Lifetime Study.

**EYE REGISTRY REPORT — JANUARY 5, 2013**

—— ELAINE AZEROLO, SCWTCA EYE REGISTRY CHAIR

**BOARD ACTION REQUESTED:**

Action is needed to encourage breeders to have eyes examined on Wheatens being bred. The number of Wheatens examined each year has dropped by more than 60% in the last 10 years. (See statistics below.)

The Code of Ethics states that eyes must be examined a minimum of every two years for dogs being bred but does not require that results be registered. Requiring registration would add accountability and provide a public record that would encourage participation.

**RECOMMENDED ACTION:**

1. I recommend that the Board establish a policy requiring registration of eye examinations as a condition for Breeders List eligibility. Registration with either of the two registries would be acceptable.

2. I recommend that the Board require annual eye exams by board-certified veterinary ophthalmologists as a condition for Breeders List eligibility.

**Rationale for Item 1:** Registration of exam results provides a public record accessible to puppy buyers, other breeders and the Club. It demonstrates that the COE requirement is being met. Registration of eye exams is a reasonable requirement for the privilege of being on the Breeders List.
Ten years ago, when SCWTCA still published the names of dogs registered, the number of dogs examined was much higher. Public disclosure is a reminder and motivator.

The cost of registration is reasonable. Fees are $12 for the initial registration and $8 for subsequent registrations. This is a lifetime total of $44 (based on current fees and COE requirements). This is a very small percentage of the price of one Wheaten puppy.

**Rationale for Item 2:** Annual exams are recommended by the American College of Veterinary Ophthalmologists (ACVO). They are the experts in this field and are the certifying board for ophthalmologists. Both eye registries follow the ACVO guidelines, and registration is in effect for only one year following the exam.

Annual exams provide a more current assessment of eye status prior to breeding. Eye conditions are not static, and vision-limiting conditions may have a late onset.

Convenience and cost factors are not adequate reasons to support a policy requiring less frequent exams. There are ACVO vets in most states and major population centers. Many kennel clubs sponsor clinics where exam costs are reasonable. And the clinics are often held at all-breed shows.

The privilege of Breeder’s List eligibility should command the highest standards for breeders. An exam every two years is listed as a “minimum” requirement in the COE. More than minimum should be expected for Breeder’s List eligibility. Being on the SCWTCA Breeders List implies excellence to the public.

**Background information:** The total number of Wheatens whose eyes are examined is decreasing. During the most recently reported three year period, 2009-2011, an average of 131 Wheaten eye exams were completed compared to an average of 296 for each of the previous three years, 2006 -2008. The number of exams averaged 348 dogs per year from 1998-2002 when SCWTCA last published lists of dogs with eye exams registered.

In addition, a large percentage of the dogs examined are young. It seems likely that many dogs are being examined only once, prior to first breeding. This means late-onset disorders may be missed. From 2006 -2011, 53% of those examined were under 3 years of age; 79% were under 5. Only 8% of those examined were over age 7 even though the COE requires eye exams through age 10. (Statistics represent exams by board-certified veterinary ophthalmologists as reported to the Canine Eye Registry Foundation.)

Hereditary eye conditions affecting vision were found in of 3.4% of 888 Wheatens examined during 2006-2008. The article, “Hereditary Eye Disease in Wheatens,” in the June 2012 issue of Benchmarks provides additional information.

**Two Eye Registry Groups:** There are currently two organizations registering eye exams by board certified veterinary ophthalmologists. The American College of Veterinary Ophthalmologists (certifying board) has endorsed the OFA Eye Certification Registry as its recommended canine eye registry beginning November 1, 2012. The Canine Eye Registry Foundation (CERF) continues to operate, and ACVO members may continue to use its registry. For owners, the process and fees are the same. More information about both registries was included in the October 2012 report. This is a recent change, and it is too soon to predict whether one registry will be a more valuable resource for data on Wheaten eye problems.

**Current CERF Statistical Reports:** CERF states that it is now current on 2012 entries and expects to have the statistical report ready in early 2013. When the 2012 results are available, 2009-2012 reports will be summarized for Benchmarks and HealthNews publication. [See p.18 of this WHN issue for the new CERF report.]

**OFA Eye Certification Registry:** This is a new registry, certifying six Wheatens in the first two months. The OFA database has continued to display CERF registrations also.
NEW EYE DATABASE AND REGISTRY AT OFA

The American College of Veterinary Ophthalmologists (ACVO) and the Orthopedic Foundation for Animals (OFA) jointly established a database to track results of canine eye examinations and a certification registry effective November 1, 2012.

The ACVO is the accrediting group that establishes requirements for becoming a Board Certified Veterinary Ophthalmologist and determines whether requirements have been met. It has endorsed use of the OFA registry. The Genetics Committee of the ACVO offers breeding recommendations for dogs with hereditary eye disorders.

The OFA Eye Certification Registry (ERC) registers dogs whose eyes are free from observable hereditary eye disease that affects vision when the dog is examined by an ACVO certified ophthalmologist. This includes dogs with “normal” eyes and those with hereditary conditions not currently known to affect vision. Data for these dogs is listed on the OFA website, available to the public.

OFA registry exams procedures and fees are the same as those used by the CERF (Canine Eye Registry Foundation). OFA eye exam forms include copies for the owner, ophthalmologist and OFA research database. To register the dog, owners send their copy of the form and a fee to OFA.

The ACVO/OFA Clinical Database for Ophthalmic Diagnoses will provide data for use by researchers and breed clubs working to determine significance of general and breed-specific eye conditions. The database will collect information on dogs examined by ACVO ophthalmologists in private practice and institutional practice as well as dogs being examined for certification. OFA has database capabilities to manage data accurately and in a timely manner.

In recent years, data processing issues have caused significant delays in CERF statistical reports to researchers and breed clubs. CERF continues to operate, and some ACVO members were using its forms as recently as February 2013. If owners have a CERF form, it may be submitted to OFA with the fee and a signed note asking that it be added to the OFA database. CERF will also register the dog if the form and fee are sent to them. For several years, OFA has listed eye registration information sent quarterly by CERF. CERF information was still being listed at OFA in April 2013. CERF does not send abnormal exam statistics to OFA.

LATEST STATISTICS FOR HEREDITARY EYE DISEASE IN WHEATENS

Eye exam results for 512 Wheatens were listed in CERF Statistical Analysis reports for 2009 -2012. Sixty-five percent of the Wheatens examined were females. Five percent were under 1 year of age; 45% were under 3 years; 76% were under the age of 5 years when examined. Eleven percent were over 8 years.

Hereditary eye disease that affects vision occurred in 4.5% of the Wheatens examined. ACVO guidelines recommend that these dogs should not be bred. An additional 4.9% had eye disorders presumed to be hereditary but not currently thought to affect vision. These dogs receive a “Breeder Option” designation listing the abnormality. ACVO recommends that if they are bred, it should be to dogs not having the same eye abnormality. As research
continues, Breeder Option conditions may be determined to be “normal” or to significantly affect vision. Breeding recommendations would be changed accordingly.

Cataracts were the most common hereditary problem affecting vision in Wheatens examined in 2009-2012. Almost three percent (2.7%) of Wheatens had significant cataracts. Cataracts are opaque areas in the lens of the eye that can cause blindness if they cover the entire lens. ACVO guidelines say “The prudent approach is to assume cataracts to be hereditary except in cases known to be associated with trauma, other causes of ocular inflammation, specific metabolic diseases, persistent pupillary membrane, persistent hyaloid or nutritional deficiencies.” ACVO recommends that these dogs should not be bred.

It should not be assumed that cataracts are a normal “old age” condition or that they occur only in older dogs. Six of the 14 Wheatens with cataracts were under the age of 3 years. Only 3 were over the age of 8 years.

Some cataracts are listed as “significance unknown” which is a Breeder Option designation. There were 44 “cataracts — significance unknown” found in 2009-2012 exams.

SCWTCA BREEDER’S LIST EYE EXAM REGISTRATION REQUIREMENT

At its January 2013 meeting, the SCWTCA Board approved a policy requiring registration of eye exams as a condition for Breeder’s List eligibility. Registration may be with either OFA or CERF.

REFERENCES:

American College of Veterinary Ophthalmologists website, www.acvo.org
Orthopedic Foundation for Animals website, www.offa.org
OFA REPORT — JANUARY 13, 2013

—KATHY EICHMAN, SCWTCA OFA LIAISON

The OFA was formed and Incorporated in 1966 and Wheaten OFA ratings started in Jan. 1974. From 1974 thru 2012, according to OFA records, a total of 5,952 Wheaten hip X-rays have been reviewed and rated by the OFA. Beginning in 2008, verification of permanent identification must be performed in order for the data to be forwarded to the AKC for inclusion in their records.

2011 — 4TH QUARTER

- Hip--------------------------------- 31 Evaluations (1 Borderline Unilateral Left, 1 Mild Unilateral Right)
- Elbow----------------------------- 7 Evaluations
- Patella----------------------------- 4 Evaluations
- Degenerative Myelopathy-- 2 Evaluations
- Eye----------------------------- 5 Evaluations

2012 OFA ANNUAL SUMMARY

Wheaten OFA’d in 2003 — 255 (6.3% Abnormal)  2008 — 144 (4.2% Abnormal)
2004 — 226 (4.4% Abnormal)    2009 — 156 (7.7% Abnormal)
2005 — 189 (2.7% Abnormal)    2010 — 138 (8.0% Abnormal)
2006 — 195 (9.7% Abnormal)    2011 — 111 (7.2% Abnormal)
2007 — 168 (6.6% Abnormal)    2012 — 131 (3.0% Abnormal)

2012 OFA ANNUAL SUMMARY

Wheaten Owners who made all results public after 2001 = 25.9%

- Hip----------------------------------135 Evaluations — 131 Normal, 4 Abnormal (26 Excellent, 92 Good, 13 Fair, 4 Mild HD)
- Elbow----------------------------- 36 Evaluations — 33 Normal, 3 Abnormal Grade 1 Dysplasia
- Cardiac----------------------------- 10 Evaluations — 10 Normal
- Thyroid----------------------------- 1 Evaluations — 1 Normal
- Patella----------------------------- 31 Evaluations — 31 Normal
- Eye------------------------------- 6 Evaluations — 6 Normal
- Baer Hearing--------------------- 0 Evaluations
- Degenerative Myelopathy-- 12 Evaluations — 4 Normal (33.3%), 5 Carriers (43.7%), 3 At Risk (25.0%)

2012 OFA ANNUAL SUMMARY

The total number of Wheatens OFA’d from 1975 - 2012 = 5,952 (4.8% Abnormal)
17.0% Excellent, 66.7% Good, 11.2% Fair, 0.3% Borderline, 3.4% Mild, 1.2% Moderate, and 0.2% Severe

Cumulative numbers and percentages from January 1975 - December 2011 are available.

ACCORDING TO THE 2013, 1ST QUARTER OFA REPORT,

- 45 Wheatens received Hip Certification
- 3 Wheatens received Elbow Certification
- 14 Wheatens received Patella Certification
- 12 Wheatens received Cardiac Certification
- 21 Wheatens received CERF Certification — a copy of the eye information was sent to Elaine Azerolo
RESEARCH OF CANINE OSTEOSARCOMA & IBD ADVANCE TREATMENT OPTIONS

—Used with permission from the Purina Pro Club Update newsletter, Nestle Purina PetCare

While there is no cure for canine osteosarcoma or inflammatory bowel disease (IBD), researchers are focusing on promising new treatments. Recent advancements in treating osteosarcoma may spare limbs and extend life for dogs affected by this painful cancer. Likewise, genetic discovery of polymorphisms causing IBD in German Shepherd Dogs may lead to new treatments. Here are snapshots of the research.

KILLING CANCER CELLS

Osteosarcoma is a fast-spreading, painful cancer that affects about 9% of giant breeds and 1% of large breeds. Owners and veterinarians work together to provide the best treatment possible using surgery, chemotherapy, radiation therapy and medications for palliative care. Usually, amputation of the affected limb followed by chemotherapy is recommended to increase survival, but owners of giant breeds often are reluctant to amputate, particularly a forelimb, because it can make walking difficult and may compromise quality of life.

While the conventional therapies for treating osteosarcoma aim to increase survival, research veterinarians are investigating promising new treatments. These include a recombinant bacteria vaccine and a powerful limb-sparing stereotactic radiosurgery that kills tumor cells and spares healthy tissue.

Osteosarcoma mostly occurs in dogs over the age of 8, long after they have been bred, but dogs as young as 1 or 2 years old can develop the cancer. Since osteosarcoma generally occurs in the leg bones, lameness and difficulty going up and down stairs are the most common signs that owners notice.

The cancer arises from mutated cells that stop bone-matrix remodeling and the production of bone cells. A definitive diagnosis is made from a bone biopsy, but characteristic lesions on radiographs are a strong indicator of osteosarcoma. Tumors are depicted in radiography as a starburst pattern of needle-like fragments of bone. In 90-95% of dogs, osteosarcomas have micrometastasized at the time of diagnosis. Micrometastasis is not clinically evident on radiographs but will eventually lead to large metastatic tumors usually in the lungs or other bones.

Treatment of osteosarcoma is challenging partly because the cancer is likely to metastasize, or spread, especially to the lungs. Metastasis in the lungs usually is the ultimate cause of death for dogs with bone cancer.

It is not known definitely whether osteosarcoma is an inherited condition in dogs. Nicola Mason, B.Vet.Med., Ph.D., DACVIM, the Pamela Cole Chair in Companion Animal Medicine at the University of Pennsylvania School of Veterinary Medicine, says, “Large and giant breeds may be predisposed to osteosarcoma because of genetic influences, but other factors may also be involved. Rapidly proliferating cells tend to be more susceptible to cancer-forming events; therefore dogs whose bones grow rapidly, such as large and giant breeds, or dogs that experience bone trauma and damage that requires cellular proliferation for repair may be at higher risk for developing osteosarcoma. Chronic inflammation is known to be associated with the development of other cancers, although it is unknown whether persistent bone inflammation predisposes to bone cancer. Most likely the cause of osteosarcoma, like other tumors, is multifactorial, involving both genetic and as-yet unknown environmental factors that together can create the perfect situation for bone cancer to develop.”

(continued on next page)
Alternative approaches to treating osteosarcoma are being investigated. Sarah Charney, D.V.M., DACVIM, DACVR, adjunct professor of radiation oncology at the University of Illinois College of Veterinary Medicine and staff radiation oncologist at Animal Specialty Center in Yonkers, N.Y., is part of a team that has pioneered a limb-sparing CyberKnife® radiosurgery technique for dogs where amputation is not possible or desired. Combined with chemotherapy, this radiosurgery, also known as stereotactic surgery, has a survival time that is similar to the standard of care with amputation and chemotherapy for good candidates. Unfortunately, not all dogs are good candidates. The viability of radiosurgery is best assessed by a CT (computed tomography) scan. The benefit of radiosurgery is that it saves the limb.

“With this procedure, a radiation oncologist uses a high-tech, image-guided and computerized robotic control system to deliver radiation with submillimeter accuracy,” Charney explains. “The CyberKnife radiation beams are sculpted to conform tightly to complex masses and deliver multiple radiation beams from many points outside the dog’s body to the targeted tumor. The beams kill tumor cells yet spare healthy tissue. When the beams converge on the tumor mass, they deliver high-energy, pinpointed radiation with astounding power.”

Compared to conventional radiation therapy, the precision of CyberKnife radiosurgery allows higher doses of radiation to be delivered to the tumor while minimizing damage to healthy tissue. One to three treatments are the same as 15-20 treatments of conventional radiation. The benefits include fewer hospital visits, fewer anesthetic episodes, and reduced stress. Treatment is based on how much bone destruction has occurred as seen on a CT scan.

Meanwhile, at the University of Pennsylvania, Mason is testing a recombinant Listeria monocytogenes tumor vaccine. “Our project focuses on finding and killing the cancer cells that amputation and chemotherapy overlook,” she says. “This method uses the body’s immune system to elicit anti-tumor immunity and prolong survival in dogs with cancer of their long bones.”

To be eligible, dogs with osteosarcoma must have had a limb amputation and standard chemotherapy consisting of four doses of carboplatin. “If the dogs live for more than eight months following vaccination, which is greater than one year post-diagnosis, then we will have increased median survival and will consider that the vaccine is having some effect,” Mason says.

“We hope in the future to test whether this vaccine is effective in dogs that have not had amputations. This technology could be applied to other cancers, such as canine mammary cancer,” she says. “It also may help people. Pediatric oncologists are watching our trial closely. This bacteria-based vaccine could possibly stimulate an immune response in children with osteosarcoma.”

While Cyberknife radiosurgery and the L. monocytogenes vaccine provide a glimpse of future treatment possibilities for osteosarcoma, owners of dogs diagnosed with the cancer today continue to struggle to determine the best treatment that will extend longevity for their individual dog.

GENETICS MAY AID IBD TREATMENTS

When a dog experiences idiopathic diarrhea and vomiting, veterinarians may suspect canine inflammatory bowel disease. The chronic gastrointestinal condition occurs more
commonly in middle-aged large-breed dogs. Since it cannot be cured, veterinarians manage IBD using medications to address the signs.

Efforts to learn more about IBD in German Shepherd Dogs led to the recent discovery of polymorphisms in the TLR4 and TLR5 (Toll-like Receptor) genes. The research was supported by the Morris Animal Foundation and the American German Shepherd Dog Charitable Foundation (AGSDCF).

Lead investigator Karin Allenspach, Dr.Med.Vet., Ph.D., head of the Clinical Investigation Center at The Royal Veterinary College of the University of London, says, “It appears German Shepherd Dogs with chronic enteropathies have a distinctly different microbiome from healthy dogs, as well as from other breeds with IBD. This includes overrepresentation of certain traditionally labeled ‘beneficial’ bacteria in the duodenum, specifically sequences of the order of Lactobacillales.

“We’ve made great progress to identify genetic predispositions underlying IBD in German Shepherd Dogs. We continue to analyze whether the mutation of an immune system protein is linked to the intestinal inflammation associated with IBD. If so, new treatments potentially could be developed. We also have identified antibodies specific for E. coli flagellin in dogs with IBD that are not present in unaffected dogs. This could lead to the development of a noninvasive diagnostic test for IBD.”

While diarrhea and vomiting are the most common signs of IBD, the disorder also may cause anorexia or loss of appetite, weight loss, and blood or mucous in the stool. With loss of appetite, a dog becomes lethargic and loses condition and coat. Signs are persistent, and by the time a veterinarian examines a dog with IBD, overall health condition may be poor.

“The clinician faced with a potential case of IBD usually performs an extensive workup to exclude extra gastrointestinal causes as well as treatable disorders, such as pancreatic diseases, chronic parasitic or bacterial infections, and tumors,” Allenspach says. An accurate diagnosis may require an endoscopic biopsy of the GI tract. A veterinarian looks for lesions caused by lymphoplasma cellular inflammation in the mucous layer of the GI tract. These can be seen in about half of cases. “The intestinal lining is composed of cells with proteins on the surface,” says Allenspach. “Some of the proteins are receptors that recognize microbes. If that protein is not functioning properly, it will tell the immune system to develop inflammation against the normal bacteria in the intestines, causing the diarrhea and vomiting that are characteristic of the disease.”

After a tentative diagnosis of IBD is determined, the gold standard approach to treatment is a food trial with an elimination diet containing a novel or hydrolyzed protein. This is based on theories that IBD is caused by an allergic reaction or hypersensitivity to dietary antigens. If a food trial does not reduce signs of IBD, antibiotic treatment is tried for several weeks, followed by immunosuppressant and anti-inflammatory treatments.

**Lymphocytic plasmacytic IBD** is the most common. It is due to an excess of two kinds of white blood cells: lymphocytes and plasma cells. Lymphocytes are responsible for much of the body’s immune protection, and plasma cells are a mature type of lymphocyte. This type sometimes responds well to a four- to five-week course of antibiotics such as metronidazole or tylosin. “These antibiotics probably are effective because they change the gut microflora,” Allenspach explains.

If antibiotics fail, the next step is anti-inflammatory drugs such as steroids, and immunosuppressants that help eliminate intestinal inflammation. “Steroids can have significant side effects,” says Allenspach, who is researching alternative medications. Cyclosporine, a drug used in humans to prevent organ transplant rejection, has shown excellent results without
the side effects associated with steroid use, e.g., excessive thirst, urination, and gastrointestinal ulcers, she says.

The second most common form of IBD, **eosinophilic gastritis or gastroenteritis**, refers to the type of inflammation found in biopsies of the GI tract. This type of IBD is more severe. Biopsies show a high number of white blood cells called eosinophils that are often linked to allergic responses and parasitic infestations.

As breeders try to understand whether they should breed dogs with IBD, veterinary experts also grapple with the question. “It is too early to say that dogs with the mutation should be excluded from the breeding pool,” Allenspach says. “It is probable that many dogs carry the mutation, but not all of them will get IBD. It is unlikely that one mutation is the single cause of the disease. There are environmental factors and probably other genetic factors that we haven't found yet.”

In most breeds, the cause of IBD is likely not strictly genetic or environmental, Allenspach says. Affected dogs within a breed probably share one or more genetic mutations, but the presence of the mutation alone does not mean the dog will develop IBD. “If the environmental triggers were known, they could be avoided; so possibly a dog carrying the mutation would never develop the disease,” says Allenspach. “This is an area needing to be studied. At this point, we really don't know.”

Meanwhile, Allenspach advises breeders not to link every dog or every breed in the same category. “My belief is that there are different triggers in different breeds and thus different responses to treatment among the breeds as well as among different dogs,” she says.

**CLINICAL TRIAL FOR IBD SEeks PARTICIPANTS**

One of the greatest challenges for the researchers working to prevent, treat, and cure canine disease is recruiting participation in research projects. **There is a research study happening in your region. Please consider helping!**

**INFLAMMATORY BOWEL DISEASE CLINICAL TRIAL**

Dr. Al Jergens and colleagues are seeking dogs suspicious for or recently diagnosed with chronic inflammatory bowel disease (IBD) to be enrolled into a clinical trial funded by the AKC Canine Health Foundation. In brief, this team is investigating whether probiotic therapy is useful in treating these dogs. This is an eight-week clinical trial where IBD dogs receive the probiotic or placebo along with traditional dietary and drug therapy.

The trial is taking place at six locations: Iowa State University, Colorado State University, Texas A&M University, University of Tennessee, Southeast Veterinary Referral Center (Miami), and San Diego Veterinary Specialty Hospital.

**LEARN HOW TO HELP!**

Also, view the complete list of studies needing participation* for other opportunities to help. Each study has unique requirements, so please contact the laboratory listed if you have questions about a specific project.

And don’t forget that samples are always being accepted by the Canine Health Information Center (CHIC) DNA Repository and the Canine Comparative Oncology and Genomics Consortium.

From all of us at the AKC Canine Health Foundation, thank you for considering participating in research!

*The AKC Canine Health Foundation ensures studies are Institutional Animal Care and Use Committee (IACUC) approved and provides standard informed owner consent information before publicizing requests for participation. Not all projects listed are funded by the AKC Canine Health Foundation; and the inclusion of information about studies does not necessarily imply a recommendation for participation. This list is provided as a service to dog owners and breeders.
Pancreatitis is almost as frustrating for doctors to deal with as it is for dog owners. It’s one of those diagnoses that is incredibly difficult to make before it’s too late. The symptoms are vague; and the current tests are hard to perform, unreliable, or both. That’s why it’s so important that researchers continue to hunt for a simple and effective way to diagnose pancreatitis. It’s not an easy task.

Diagnostic tests are evaluated on two criteria: sensitivity and specificity. The sensitivity of a test measures how good it is at detecting dogs that have the condition it’s looking for. A diagnostic test for pancreatitis with a sensitivity of 85% would correctly identify 85 out of every 100 dogs with pancreatitis as having the disease. In contrast, the specificity of a test measures how well it identifies dogs who don’t have the condition of interest. A diagnostic test for pancreatitis with a specificity of 90% would correctly identify 90 out of every 100 healthy dogs as not having pancreatitis.

The thing is, the usefulness of a test depends on not just sensitivity and specificity but how common a condition is in the population where the test is being used. After all, in the vet’s office, you don’t know if any dog has pancreatitis or not — that’s what you’re trying to find out. However, if you know how common pancreatitis is and the sensitivity and specificity of the test you’re using, you can determine its positive predictive value — the likelihood that any positive test you get is actually accurate. That’s important because you don’t want to treat a dog for pancreatitis if you don’t need to, but you do want to intervene if it will help. A positive predictive value of 85 tells you that 85 out of every 100 dogs who test positive are actually sick — a much more valuable statistic for the clinician than the sensitivity. In fact, it turns out that the positive predictive value is actually far more dependent on the specificity of the test than the sensitivity in most circumstances.

All of that explains why, with the help of support from the AKC Canine Health Foundation, researchers from the University of California—Davis recently set out to investigate the sensitivity and specificity of a new blood test for pancreatitis and compare it to several other blood tests that might be useful in detecting the disease. The developers of the test, known as the Spec cPL, had determined its sensitivity as 63.6%; but they hadn’t figured out how specific it was, which meant it was difficult to tell how accurate any positive results might be. One previous study had investigated the same question, but more data was clearly needed.

They got it. The scientists found that the Spec cPL was relatively sensitive and specific, depending on the specific cutoff values used for the tests. There was a tradeoff, as there often is, found when they chose different cutoff levels — increasing the sensitivity of the test came at the expense of specificity, and vice versa. However, Spec cPL clearly provided better diagnostic results than any of the other tests they tried, giving hope that it might one day ease the diagnosis of canine pancreatitis. Further research is still needed, particularly as the study contained few dogs with healthy pancreases which could affect the calculated specificities. Still, this research moves us one step closer to a reliable blood test for canine pancreatitis — a safer, easier way to start treatment and improve the quality of dogs’ lives.

**SCIENTIFIC PUBLICATION:**

Dogs love to run and jump, whether they are agility competitors or just chasing toys, and their joints can take a pounding. Joint problems fall into two general categories: degenerative problems, such as arthritis, and developmental problems, including hip and elbow dysplasia.

For this in-depth report, DOG FANCY consulted experts to help you recognize and deal with both hip and elbow dysplasia, provide you with a close look at the PennHIP test and how it detects joint problems in the hips, and let you know what to expect if your dog gets elbow dysplasia.

Hip Dysplasia and PennHIP

By Meredith Wargo

Hip dysplasia is the most commonly inherited orthopedic disease in dogs. This improper formation of the hip joint usually leads to osteoarthritis, which causes joint damage, inflammation, and pain. Dog owners spend $800 million to $2 billion annually in treatments for their pets who suffer from this debilitating disease, according to a publication in preparation from the University of Pennsylvania Hip Improvement Program, or PennHIP. Although no cure exists, tests help identify dogs who are susceptible to developing hip dysplasia. Early detection can aid in treatment and help breeders screen for the disorder.
X-rays are the only definitive means to diagnose the disease. For more than 40 years, the Orthopedic Foundation for Animals has regulated the screening, which consists of taking an X-ray of an animal’s hips in a certain position. The single hip-extended film is evaluated by three board-certified veterinary radiologists, who rate the condition of the hips and assign them a grade, from excellent conformation to severe hip dysplasia.

If the consensus of the three evaluations results in an excellent, good, or fair rating, the dog receives an OFA registry number. This information is entered into the OFA hip dysplasia database that functions as a voluntary screening service, which increases the probability for obtaining a dog without the condition for breeding, competition, or as a healthy pet.

“The OFA maintains a verifiable public database,” says G. Gregory Keller, D.V.M., M.S., diplomate of the American College of Veterinary Radiology and chief of veterinary services for the OFA in Columbia, Mo. “If you are looking to purchase a dog and have sire and dam information (registration name or number), you can verify that what you’re being told about the animal is correct.”

In 1993, a procedure called PennHIP was developed to better assess a dog’s risk for developing the disease. “PennHIP improves our ability to measure hip laxity,” says Gail Smith, VMD, Ph.D., professor of orthopaedic surgery and founder/director of PennHIP at the University of Pennsylvania School of Veterinary Medicine in Philadelphia. The laxity, or looseness, of the hip joint is what leads to osteoarthritis.

→ What is canine hip dysplasia? Canine hip dysplasia is the abnormal development of a dog’s hip, and is associated with looseness of the hip joint. In a dog’s hind legs, the head of the femur, or thighbone, is shaped like a ball and is designed to fit tightly into the acetabulum, or socket. Dogs with hip dysplasia have looser or more moveable hip joints.

→ What are the signs? Hip dysplasia can be detected as early as 4 months of age. Symptoms may first appear as a swaying or unsteady gait. As the disease progresses, some dogs may move their hind legs together in what is described as “bunny hopping.” Others may exhibit difficulty navigating stairs or rising from a sitting position. A distinct clicking sound can often be heard when the animal is walking or running.

→ Who’s at risk? While gender doesn’t seem to be a factor, size is. The disease is more common in large-breed dogs than in smaller breeds. Bernese Mountain Dogs, English Setters, Golden Retrievers, German Shepherd Dogs, St. Bernards, Standard Poodles, and Rottweilers are breeds that are commonly afflicted. However, dogs of all breeds and sizes are susceptible to this inherited condition.

→ How is it treated? Non-steroidal anti-inflammatory drugs and dietary changes, such as increasing the consumption of omega-3 fatty acids, can help decrease the inflammation and discomfort associated with this disease. A surgical option once a dog reaches maturity is total hip replacement. “The smaller the dog, the less it is probably needed, although nano total hip replacements (implants for animals generally weighing less than 10 pounds) for Poodles have been described with about 90 percent return to normal,” says James Rouse, D.V.M., Doughtman Professor of small animal surgery at the Kansas State University College of Veterinary Medicine. “Total hip replacement is definitely the best for any dog weighing more than 40 pounds.”
Instead of the traditional method of taking a single X-ray view, PennHIP consists of three separate X-rays: the distraction view, the compression view, and the traditional hip-extended view. The distraction and compression views are used to provide accurate measurements of joint laxity and congruity — the degree to which the hip components fit together — while the hip-extended view is used to provide supplementary information regarding the existence of osteoarthritis in the hip.

What’s more relevant, Smith says, is that the hip laxity measurement from the distraction view X-ray — taken only during the PennHIP procedure — is more closely associated with a dog’s likelihood of developing osteoarthritis than is the laxity measurement from the hip-extended-view X-ray — taken during both the OFA and PennHIP procedures.

To X-ray the various positions of the hips in the PennHIP procedure, the dog must be anesthetized or deeply sedated, which is not required under the OFA screening. However, the OFA does recommend that dogs receive chemical restraint, or anesthesia, to the point of relaxation.

“The vast majority of veterinarians do sedate,” Keller says. “It’s a comfort level for both the veterinarian and the owners. It’s also easier to get the dog positioned properly with sedation. But since it’s an elective procedure, some owners don’t want their pets chemically restrained.”

One of the advantages of PennHIP is that it can be reliably performed on puppies as young as 16 weeks old. Dogs of this age can receive hip grades from veterinary radiologists at the OFA, but are not eligible for independent evaluation by three board-certified radiologists until 2 years of age.

“(Evaluation with PennHIP at a young age) provides essential information for choosing service dogs, breeding dogs, or pet dogs,” Smith says. In breeding dogs, he adds, it would be wise to double-check hip status several times during a dog’s breeding life. “We know that osteoarthritis of hip dysplasia is strongly age-dependent, so it’s important to radiograph older dogs to learn the reliability of our earlier predictions.”

While the OFA screening can be used by any licensed veterinarian with access to an X-ray machine, veterinarians must complete specialized training before becoming certified to perform PennHIP. These vets submit X-rays of every PennHIP patient to the University of Pennsylvania for evaluation and inclusion in a database. The PennHIP database consists of 109,000 dogs, approximately 35 percent of which are from dog breeders, according to Smith. “The strict use of the PennHIP method, along with other tools such as estimated breeding values, has allowed some working dog agencies to eliminate hip dysplasia as a concern,” he says.

For example, in the 1980s, Smith approached The Seeing Eye Inc., the oldest existing guide dog school in the world, to request its participation in helping him develop PennHIP procedures. In 1995, The Seeing Eye began using PennHIP as part of its selection process for breeding dogs.

“We use PennHIP to discern differences among the dogs that we are considering for breeding with respect to hip quality,” says Eldin Leighton, Ph.D., Jane H. Booker Chair in Canine Genetics at The Seeing Eye Inc. in Morristown, N.J. “PennHIP is a completely different look at the structure of the hip in contrast to the extended view score. When we look at the range of values we get from PennHIP, even among dogs that on the OFA scale have excellent hips, we still find a range in PennHIP values.”

“PennHIP provides us a basis for choosing our replacement breeders with respect to hip quality, which in turn helps give our dogs a longer working life,” Leighton adds.

As with other medical tests, many owners may be concerned about the cost of hip dysplasia screenings. PennHIP is more expensive, usually at least 30 to 50 percent more, according to James Roush, D.V.M., M.S., diplomate of the American College of Veterinary Surgeons and Doughman Professor of small animal surgery at the Kansas State University College of Veterinary Medicine in Manhattan, Kan. Prices for both the PennHIP and OFA procedures can vary depending on the veterinarian, however.

“We don’t have data on what our PennHIP members charge clients for performing the service,” Smith says. “Here at
Elbow Dysplasia

By Phil Zeltzman, D.V.M.

Cavo, a 6-month-old German Shepherd Dog, was perfect in every way, until he started to limp on his left front leg. “It was subtle at first, then the pain progressively became worse,” recalls his owner, Sandy Dougherty, who lives near Hazleton, Pa. A physical exam performed by his family veterinarian revealed pain and swelling in Cavo’s left elbow. X-rays under sedation showed a problem with his elbow, a condition called ununited anconeal process. The verdict: Cavo needed surgery to remove the piece of bone that was causing the pain.

Ununited anconeal process is one of three conditions of the elbow generically called “elbow dysplasia.” As with hip dysplasia, elbow dysplasia stems from poor alignment between the bones. The elbow is a complex joint that involves three bones: the humerus in the arm; the radius, the main bone in the forearm; and the ulna, a small but important bone in the forearm. If all three bones are not perfectly aligned, problems with the bones and the cartilage can follow.

The cartilage at the bottom of the humerus, for example, can have a defect called osteochondritis dissecans. The flap of cartilage may be completely separated or only partially attached to the bone in dogs with this condition.

The ulna, on the other hand, can present two conditions. One is Cavo’s condition, or ununited anconeal process, in which a large section of the bone does...
Supervised swimming can be a beneficial activity for a dog with elbow dysplasia, as long as the dog doesn’t struggle getting into or out of the water.

not attach to the main part of the ulna inside the elbow joint. The third type of elbow dysplasia, known as fragmented coronoid process, occurs when a small piece of bone called the coronoid process separates from the inside part of the ulna.

In all three situations, as the piece of cartilage or bone moves inside the joint, the dog experiences pain and swelling. Usually between 4 and 6 months of age, elbow dysplasia causes lameness, weight shifting to other legs, reluctance to move or play, stiffness, and muscle wasting. Without treatment, the signs get worse, and the dog ends up with severe arthritis.

Most affected dogs are large and giant breeds, such as German Shepherd Dogs, Labrador Retrievers, Golden Retrievers, Rottweilers, St. Bernards, and Newfoundlands.

Sedation is often critical to obtain quality X-rays. Even then, diagnosis is not always easy, and advanced imaging such as a CT scan or an MRI may be required. It is important to always check the other elbow, even if no signs can be detected, as elbow dysplasia can occur in both joints. Fortunately, Cavo’s right elbow was normal.

“With either condition, the initial treatment in a young dog is typically surgery,” explains Justin Harper, a board-certified veterinary surgeon at Texas Specialty Veterinary Services in Boerne, Texas. Through a short skin incision or with an arthroscope — a tiny camera placed in the joint — the piece of cartilage or bone is removed, most commonly by a veterinary surgeon. “In older dogs, when severe arthritis and pain cannot be controlled, a total elbow replacement can be performed,” Harper says.

After surgery, or if your veterinarian does not recommend surgery, several treatment methods can help increase comfort and slow down arthritis. Options include rest, weight control, pain medications, physical therapy, and joint supplements. Once the puppy is fully grown, your vet can recommend an “arthritis diet” enriched in omega-3 fatty acids.

You’ll need to minimize your dog’s explosive activity, and encourage controlled exercise such as slow leash walks. Supervised swimming can also be beneficial, as long as your dog doesn’t struggle getting into or out of the water.

Because elbow dysplasia is partially genetic, affected dogs should be spayed or neutered. The same reasoning applies to their parents and siblings. Except through careful genetic selection, elbow dysplasia is difficult to prevent. A balanced diet, appropriate for large-breed puppies, is important so your dog doesn’t grow too rapidly.

Elbow dysplasia is a painful, debilitating, slowly deteriorating condition. The secrets to a successful outcome are early diagnosis and early treatment. Think of elbow dysplasia as having a pebble in your shoe. The sooner the pebble is removed, the better you feel and the less damage there is to your skin. Fortunately for Cavo, his family veterinarian and owner did not procrastinate, and elected for early surgery. A few months later, Cavo made a full recovery, just in time to frolic in the snow. DF

PHIL ZELTZMAN, D.V.M., CVJ, diplomate of the American College of Veterinary Surgeons, is a traveling board-certified surgeon near Allentown, Pa. (www.drvzeltzman.com). He is the co-author of Walk a Hound, Lose a Pound (Purdue University Press, 2011; www.walkahound.com).
Certain foods and household products can be dangerous to dogs!

It’s only natural for dogs to be curious. But their curiosity can get them into trouble when they get into areas where you store household items such as medicine and detergents. Many common household items that you use everyday can be harmful, and sometimes even lethal, to your dog.

**Foods that are harmful to your dog:**

- May cause vomiting, abdominal pain and/or diarrhea:
  - Wild cherry
  - Almond
  - Apricot
  - Balsam Pear
  - Japanese Plum

- May cause varied reactions:
  - Yeast dough
  - Coffee grounds
  - Macadamia nuts
  - Tomato and potato leaves and stems
  - Avocados
  - Onions and onion powder
  - Grapes
  - Raisins
  - Chocolate
  - Pear and peach kernels
  - Mushrooms (if also toxic to humans)
  - Rhubarb
  - Spinach
  - Alcohol

**Common household items that are harmful to your dog:**

- Acetaminophen
- Antifreeze and other car fluids
- Bleach and cleaning fluids
- Boric acid
- Deodorants
- Deodorizers
- Detergents
- De-icing salts
- Disinfectants
- Drain cleaners
- Furniture polish
- Gasoline
- Hair colorings
- Weed killers
- Insecticides
- Kerosene
- Matches
- Mothballs
- Nail polish and remover
- Paint
- Prescription and non-prescription medicine
- Rat poison
- Rubbing alcohol
- Shoe polish
- Sleeping pills
- Snail or slug bait
- Turpentine
- Windshield-wiper fluid

Symptoms of possible poisoning are: vomiting, diarrhea, difficult breathing, abnormal urine (color, aroma or odor, frequency, etc.), salivation, weakness. If your dog should ingest harmful chemicals, contact a veterinarian or poison control center immediately.
ACUTE KIDNEY INJURY IN DOGS

The kidneys, along with the brain and heart, are among the body’s most important organs. They keep the blood clean and balanced by filtering out waste products and excess water. These wastes occur from the normal breakdown of tissues and food. The kidneys regulate other body processes such as electrolyte balance. They produce three important hormones: erythropoietin which stimulates red blood cell production, renin which controls blood pressure, and calcitriol which is involved in calcium metabolism and keeping bones healthy.

Damage to the kidneys, sometimes called renal disease, can be very serious if enough renal tissue is affected. There are several things that can cause kidney damage, from drugs, to toxins, to infections. Kidney disease can be sudden (acute), or it can occur over time (chronic renal disease). So what causes acute kidney injury (AKI) in dogs?

CAUSES OF AKI

Leptospirosis is a bacterial, worldwide disease that can also affect humans. Dogs are usually exposed by contact with the urine of affected animals, often wildlife, or by drinking contaminated water. There is a vaccine that can protect dogs from four strains of Lepto.

Antifreeze toxicity is another common cause of renal damage. Dogs like the sweet taste, and ingesting even a small amount can affect the kidneys. They are often exposed to the antifreeze by licking the garage floor where the car radiator has leaked.

Drugs can cause kidney damage; NSAIDs, some antibiotics, and heart medications have been incriminated. Non-steroidal anti-inflammatory drugs (NSAIDs) can cause renal damage, especially if overdosed. This most frequently happens when a dog, receiving a chewable form for arthritis, chews up and eats the whole bottle of pills! Be sure these bottles are out of reach of all your pets. A class of antibiotics called aminoglycosides can cause kidney damage if overdosed or if the dog is dehydrated. Heart medications can stress the kidneys, as well as the heart disease itself can stress the kidneys. Heart patients on meds will usually have their kidney function checked regularly.

A bad infection of the kidneys called pyelonephritis will cause renal damage. A variety of bacteria can cause this. Cultures of the urine are important to determine which antibiotics are effective, then to assess if and when the infection resolves.

Foods and treats can even cause kidney damage. Raisins, grapes, and currants can cause kidney damage, although the toxin is unknown. It does seem to be from the flesh of the fruit and not the seed. Even just a handful of grapes has sickened dogs.

The chicken jerky treats from China have sickened, and even killed, hundreds of dogs. The FDA has released warnings, but the treats are still available on the market. There has been a great deal of study and inspection of facilities in China, but the toxin has still not been identified. There are reports that the duck jerky and veggie jerky treats may also cause kidney disease.
WATCH FOR SYMPTOMS

Symptoms of acute kidney disease are vomiting, lethargy, poor appetite or not eating at all, possible diarrhea, not passing urine, or possibly urinating more volume than normal. Depending on the cause, there may be fever and abdominal pain.

Treatment always includes hospitalization and intravenous fluid therapy. Time is critical as the longer the disease process endures, the more kidney tissue damage may occur and may become permanent. If it is possible that your dog ingested antifreeze, call your emergency hospital right away as there is an antidote but it needs to be administered within a few hours. Other treatments, depending on the cause, may include antibiotics and drugs to control nausea.

If you suspect your dog may have developed kidney damage, an examination, blood tests, and urine tests are in order. Your veterinarian can diagnose and treat your dog. Better yet, discuss with your veterinarian methods to try to prevent kidney damage!

SOURCES:


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CANINE VACCINATION PROTOCOL — 2012 — FOR MINIMAL VACCINE USE

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Note: The following vaccine protocol is offered for those dogs where minimal vaccinations are advisable or desirable. The schedule is one I recommend and should not be interpreted to mean that other protocols recommended by a veterinarian would be less satisfactory. It's a matter of professional judgment and choice.

<table>
<thead>
<tr>
<th>Age of Pups</th>
<th>Vaccine Type</th>
</tr>
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<tbody>
<tr>
<td>9 - 10 weeks</td>
<td>Distemper + Parvovirus, MLV (e.g. Merck Nobivac [Intervet Progard] Puppy DPV)</td>
</tr>
<tr>
<td>14 – 16 weeks</td>
<td>Same as above</td>
</tr>
<tr>
<td>20 weeks or older, if allowable by law</td>
<td>Rabies</td>
</tr>
<tr>
<td>1 year</td>
<td>Distemper + Parvovirus, MLV</td>
</tr>
<tr>
<td>1 year</td>
<td>Rabies, killed 3-year product (give 3-4 weeks apart from distemper/parvovirus booster)</td>
</tr>
</tbody>
</table>

Perform vaccine antibody titers for distemper and parvovirus every three years thereafter, or more often, if desired. Vaccinate for rabies virus according to the law, except where circumstances indicate that a written waiver needs to be obtained from the primary care veterinarian. In that case, a rabies antibody titer can also be performed to accompany the waiver request. See www.rabieschallengefund.org.
HEMORRHAGIC GASTROENTERITIS…A DEADLY SYNDROME

The following is Brandy’s story and is shared by the Angelini Family in the hopes that other Wheaten owners can learn from their tragedy.

My name is Bob Angelini. About 5 1/2 years ago, we bought a Soft Coated Wheaten Terrier puppy for a family pet. I never owned a pet before and was dead set against getting a dog. It turned out to be the best family purchase we ever made. Brandy was a huge part of our family. She unfortunately died last week. We are all devastated with the loss. There is a hole in our hearts and life that will never be filled again. To us, Brandy wasn’t a pet. She was family. She was always with us. We never took a family vacation without her. She was the neighborhood’s best friend. Kids and adults while on their walks would stop and play with Brandy. I don’t know who had more fun — the neighbors who stopped and played with Brandy, or Brandy herself, or us just watching Brandy having fun playing with everyone. My youngest son, Nick, is lost without Brandy. They were best friends and inseparable. The reason for my email is to let you know what Brandy died from; and, hopefully, you will let other Wheaten owners know of the disease and what to look for so other families won’t have to go through what we are going through.

Sincerely,

Bob Angelini

This is what Brandy died from. She went to bed happy and healthy at 10 p.m.; and, by 3:30 a.m., she was throwing up and had severe bloody diarrhea. We rushed her to the animal hospital, but she died a few hours later.

HEMORRHAGIC GASTROENTERITIS (HGE)

Hemorrhagic gastroenteritis is a syndrome in dogs characterized by a sudden onset of severe bloody diarrhea, projectile vomiting, listlessness and dehydration. Due to loss of fluids, hypovolemic shock can occur quickly. This syndrome affects adult dogs of all breeds, but tends to be more common in smaller breeds (e.g. Dachshunds, Yorkshire Terriers, Miniature Schnauzers, etc…). Most affected dogs have been healthy with no recent environmental changes.

Risk factors and cause for hemorrhagic gastroenteritis are unknown. However, there has been speculation that the problem is caused by an overgrowth of Clostridium bacteria in the small intestine. Research is ongoing. Clinical signs often begin with depression, vomiting, and lack of appetite (anorexia) followed by bloody diarrhea. Pets may be painful on abdominal palpation. Pets may or may not have a fever. Signs progress rapidly to dehydration and shock.

Differential diagnoses for these symptoms are parvovirus and other viruses, bacterial enteritis (bacterial infection of the intestinal tract), gastrointestinal ulcers, intestinal parasites, rat poisoning, intestinal obstruction or intussusception, hypoadrenocorticism, and pancreatitis. To determine the cause of the illness, your veterinarian may need to do bloodwork, fecal analysis, and possibly x-rays/ultrasound of the abdomen.

With prompt veterinary care, most dogs respond to treatment and recover. Treatment for hemorrhagic gastroenteritis involves fluid therapy. This may be done with subcutaneous fluids on an outpatient basis, or in the hospital with IV fluids. The type of fluid therapy recommended will depend on the severity of each individual case. Fluid therapy allows for correction of dehydration and replacement of ongoing fluid and electrolyte losses. Antibiotics (continued on next page)
and medications for nausea and vomiting are also sometimes helpful. Initially, the patient will be held off food and water until vomiting is under control. During the recovery period, we recommend feeding a bland diet for several days.

With appropriate treatment, most dogs make a rapid and complete recovery from hemorrhagic gastroenteritis. However, in rare cases, there can be further complications such as increased liver enzymes, bleeding disorders, seizures, cardiac arrhythmia, or even sudden death. Early and appropriate diagnosis and treatment are essential when dealing with this disease! Approximately 10% of affected dogs will have future episodes of hemorrhagic gastroenteritis.

EDITOR’S NOTE, Courtesy of Molly O'Connell: My dog, Spice, had the sudden onset of HGE. She woke one morning, didn't want to eat and seemed listless. After refusing food, she had bloody diarrhea. I raced her to the vet where she was immediately put on IV fluids. Tests showed that she had HGE. In her case, she did run a fever for several days. After four days in the hospital, she returned home. I started her on a bland diet, and she quickly recovered with no lasting side effects. Spice was a year old when she was sick and is now four and healthy. I think time was on my side because I got her to the vet immediately, and he knew how to treat her. This is one instance of a happy ending.

BUDDY’S STORY

Thursday, April 3, 2008 started off like any other routine day. By that afternoon, the day proved to be anything but routine.

My husband and I had decided to bathe our loveable, sweet, goofy, seven-year-old Wheaten Terrier, Buddy. The bath and blow dry went as expected, with Buddy trying his best to be as uncooperative as possible. In the bathtub, Buddy would hide his face in the far corner of the tub, hoping somehow if he couldn’t see us, then we shouldn’t be able to see him. On the table, Buddy would sit, hoping that we might forget to dry that hidden portion of his body.

With the bath and blow dry behind us, I decided that Buddy was in need of a trim. Everything was routine, until I turned over his front paw. Between his pads was a black, bubbly, large, angry-looking growth. I immediately knew that something was terribly wrong.

We called the vet’s office, but they were just closing. Luckily, there was an open appointment for the next morning. At the appointment, the veterinarian took one look at Buddy’s paw and confirmed our worst fears: that the growth didn’t look good.

As we waited for the biopsy results, the next few days became a blur of tears and unanswerable questions. Should we put Buddy down? If the bad part of his foot were removed, would walking be difficult? How much of the foot would they have to remove? What if they needed to remove more than the foot? How long would he live? How much pain would he have to endure? And how much would this cost us?

The biopsy results confirmed that Buddy had malignant melanoma. By the time we received the results, we had decided that we would do whatever we could to try and save our loveable little Wheaten.

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We had little time to rethink our decision, as the malignancy incredibly seemed to have grown in the few days since it was discovered. Within the week, Buddy’s toe and pad were removed. His foot remained bandaged for a long time, and he managed to hobble around without too much difficulty.
During this time, we learned that an experimental immunotherapy treatment for dogs with malignant melanoma was being offered throughout the country. At this point, we had to make another decision. Do we move ahead with the treatment or live with the results of the surgery and hope for the best? Our decision was to go forward with the treatment.

It was a two-year process involving a series of simple injections of Oncept Melanoma Vaccine. Initially, Buddy received one treatment a week for four weeks. After that, we brought him in every six months. Regular local care by our veterinarian was also an important factor in maximizing the effectiveness of the vaccine. Buddy experienced no adverse side effects as a result of the immunotherapy. It has been four years since Buddy’s initial diagnosis. Today, he is cancer-free, happy, and healthy.

When a pet becomes seriously ill, we all want to do what is best. Sometimes, that can mean putting a pet down. At the same time, the right approach is not always easy to ascertain — and results will vary — to be sure. For us, the difficult decisions we made have resulted in a longer and healthier life for Buddy.

Wishing you all the best,
Mark and Linda Anderson
Newport Beach, California

CHESTER’S STORY… A LIFE TOO SHORT…

— Miriam Kahan, PhD, MPH

When Chester (Ch Starlight Treasure Chest ROM) was three days old, I went to visit him; and my eyes went right to him (he was in a litter of 8). I picked him up and told him, ‘You will be going home with me for life in a couple of months.’ He was the pick of the litter, and he did indeed come home with me for life. Unfortunately, that life was far too short. Chester died in my bed before I could get him to the vet on February 20, 2013…four days after his tenth birthday.

On February 4, 2013 I took Chester to the vet because he had a bout of diarrhea and some vomiting for about three days. The vet gave him some IV fluids in case he was dehydrated. We ran full blood and urine testing, of course; and his BUN and creatinine were exceedingly high. Thinking it may have been that way due to an infection since all prior blood work was totally normal, we were going to retest in a couple of weeks. I was sent home with much medication (four different ones), and made a few more vet trips for administering fluids. I was also giving him saline injections and such at home.

He got better for a short bit: went to his usual pet therapy and took walks; and then around February 14th, he stopped wanting to eat, was listless and such. No matter what I fed him, he would not eat and I had to force feed him.

On February 20, I made an appointment with the vet as his eyes told me bad thoughts. He died in my bed before going to the vet. I, of course, followed the necropsy protocol. As a stud dog owner, I felt an overwhelming sense of responsibility and guilt, even though I knew I had done everything I could. I wrote a letter to anyone who had bred to him and to those puppy people who I knew.

To give you a brief summary of Chester’s health history; he was tested annually. He was not sick at all (except he was prone to torn pads every now and then), was a hearty eater and such. Here’s a brief synopsis of the last three years. All tests were done at the same vet and using the same laboratory services.

(continued on next page)
2011: All blood work was normal when testing was done.

(June) 2012: All blood work was normal including urine protein:creatinine ratio when testing was done. The UPC was very slightly high normal and was planning to test sooner than one year later.

(February) 2013: Note these tests were done less than 8 months after the 2012 tests were done. BUN and creatinine were extremely high and very abnormal.

(February) 2013 PLN-DNA test results showed that Chester was homozygous positive, carrying two copies of the variant alleles associated with PLN.

Necropsy: There were changes consistent with PLN and endstage chronic renal disease. The kidney showed there was mild to moderate multifocal to regionally extensive chronic lymphophasmacytig pyelonephritis, with moderate to marked fibrosis.

I tried to find answers, spending many hours with my vet, sharing the history of his blood work with colleagues and friends who were familiar with this all. I could not stop thinking about how quickly all of this developed.

I am still devastated four months later. Usually quite a strong person, I feel my personality has changed since this has occurred. I feel my spirit has left me. I joined a pet bereavement group. I reassessed my finances after spending over $3000 the last two weeks of his life. But, my emotional state or my own loss is not why I write this article. I write this in hopes that it emphasizes how vigilant we should be with dogs with markers and how fast PLN can progress.

15 TIPS FOR FIREWORKS (AND THUNDERSTORM) HAPPINESS
— PHIL ZELTZMAN, DVM DACVS CVJ

Typical signs of a frightened pet include: hiding, shaking, drooling, trying to escape, not eating, peeing in odd places, diarrhea. Dogs can also bark or howl.

Keep in mind that while some of these tips may sound obvious to you, July 4th is one of the busiest days at emergency vet hospitals nationwide. Please don’t spend your day or evening at the ER, so read on....

Incidentally, the suggestions below also apply to pets who are scared of thunderstorms - a common occurrence in the summer.

Here are 15 tips to decrease the stress level of shaky pets during these stressful times.

1. Keep pets sheltered indoors.
2. Provide a crate or a hiding place.
3. Turn the radio or TV on to drown out the noise. However, some people disagree with this and insist that it will only add noise to the mix, while the pet will still hear fireworks or thunder. I'd say it's worth trying with your pet.
4. Never leave pets alone outdoors, even (especially) if tethered or in a fenced-in yard. Dogs especially may escape and become lost. They might injure themselves by chewing on their leashes or choking on their collars.
5. Double check your pet’s ID: whether it is a tag with a (current) phone number, a microchip or a tattoo.
6. Don't walk your dog when fireworks are being set off. Do it before they start.
7. Do not take your pet to a fireworks show. Yet I see this being done every year...
8. Don’t leave your dog in your car unattended. Not only will the noise nearby be frightening, but there is a serious risk of heat stroke — even at night — even if you crack the windows open. Please watch this fascinating video made by my colleague Dr. Ernie Ward. It may open your eyes to this classic and deadly danger: http://www.youtube.com/watch?v=Jb0cCQ-y30Y
9. If you must be outside with your pet, be sure to keep him/her on a tight leash or in a carrier.
10. Protect animals from children (of any age...) who may not realize that waving sparklers or setting off firecrackers could upset a family pet.
11. Keep your pet’s collar on, even indoors, with current ID tags, so you can be reunited more easily in the event (s)he runs away.
12. Talk to your veterinarian about prescribing a mild sedative or tranquilizer to calm the fears of an extremely stressed dog or cat. A colleague recommends a product called Composure. It can help with fireworks anxiety, as well as during thunderstorms and car rides, both in cats and dogs. OK, it may be too late for this time, so it may be worth remembering for next time...
13. You may want to try the ThunderShirt (www.thundershirt.com). It doesn’t work for every pet, but seems to help many.
14. Make sure your dog does not have access to fireworks. If a dog chews on them, they can cause serious trouble as they are loaded with heavy metals and other dangerous chemicals.
15. July 4th is about more than fireworks. It’s also a day to remember and celebrate and ... barbecue. This is a classic source of trouble for pets, including burns, bones and corn cobs stuck in the intestine, as well as pancreatitis from fatty food.

Please be safe, and happy July 4th to you! [and, of course, during stormy weather...]

*Editor’s Note: If you would like to subscribe to Dr. Zeltzman’s free newsletter, visit his website at http://drphilzeltzman.com/Free_newsletter.html.*
Please remember to test your Wheaten, at least annually. Our health researchers currently recommend that annual testing include a Complete Blood Count (CBC), Super Chemscreen, Urinalysis, and Urine Protein:Creatinine Ratio. Additional screening tests available include the Heska ERD Test, the MA (microalbumin) Test, and the Fecal API Test. Printable Testing Protocols designed for Wheaten owners and also for their own veterinarians can be found on the SCWTCA website at www.scwtca.org.

Retest your Wheaten, according to your veterinarian’s advice, if any result indicates a cause for concern.

It is essential that you track your Wheaten’s test results and watch for any trends! Early diagnosis of all health problems — including, but not limited to, kidney issues — is vital for a positive prognosis.

An easy-to-use, online Health Tracker is available with a $10 donation to the SCWTCA Endowment Fund (www.wheatenhealthendowment.org).

Please send your donation to: SCWTCA Endowment Fund, c/o Toni Vincent-Fisher, Treasurer, 3825 132nd Avenue NE, Bellevue, WA 98005.

You then get the Health Tracker by emailing Anna Marzolino at marzolinoam@aol.com. Anna is also available to help with any questions about how to input data into the Health Tracker.

The Board of the Soft Coated Wheaten Terrier Club of America and the Endowment Board thank everyone for their generous donations. Donations either fund grants selected by the SCWT Endowment Fund Board or provide matching funds for grants approved by the American Kennel Club-Canine Health Foundation (AKC-CHF).

Send your contribution to: Toni Vincent-Fisher, Treasurer, 3825 132nd Avenue NE, Bellevue, WA 98005. Make check payable to “SCWTCA Endowment” (US funds only), or contribute online (www.wheatenhealthendowment.org/endowmentform.html).

The Board of the SCWT Genetic Research Project thanks everyone for their generous donations to the fund! See http://scwtgrf.org for the current fundraisers.

The SCWT Genetic Research Fund (GRF), in cooperation with the AKC CHF, sponsors genetic research into the canine genome that is specifically aimed at identifying the genes responsible for the transference of protein-wasting diseases. This information will make it possible to develop testing protocols that will identify PLE/PLN in Wheatens.

The SCWTGRF is a 501c3 foundation. To join our effort and make a tax deductible donation, send your check payable to “SCWT Genetic Research Fund” to: David Ronsheim, Project Financial Officer, 17827 Fireside Drive, Spring, TX 77379-8017.

Or, visit our website (www.scwtgrf.org) to make an online donation through PayPal.