Researchers Relate Serotonin Gene to Compulsive Disorders in Dobermans

Up to 30 percent of Doberman Pinschers have compulsive tendencies, such as blanket and flank sucking. The behaviors, which are unique to Dobermans, are considered inherited disorders that are likely encoded in the primitive areas of the brain.

New findings by researchers at the Cummings School of Veterinary Medicine at Tufts University along with colleagues from the University of Massachusetts and the Van Andel Institute show structural differences in the brains of affected Doberman Pinschers compared to unaffected Dobermans. These differences affect specific regions in the brain similar to those in people who suffer from hoarding, a type of obsessive compulsive disorder (OCD).

The discovery by the Tufts researchers in 2009 of a mutation in the neural cadherin-2 (CDH2) gene on chromosome 7, believed to be linked to canine compulsive disorder (CCD), is now thought to provide a hereditary foundation for compulsive behaviors. The same gene has recently been confirmed by other researchers to be associated with compulsive tail-chasing behavior in the Belgian Malinois.

Modifier genes may impact the expression of the CDH2 gene, altering the severity of the condition. “Some of the suspect modifier genes seem to involve the serotonin system,” explains Nicholas Dodman, BVMS, DVA, DACVAA, DACVB, founder of the Animal Behavior Clinic at the Cummings veterinary school.

“Our latest research shows significant genetic differences between dogs that are mildly and severely affected, and the differences appear to lie in a cluster of genes that regulate serotonin.”

Dobermans affected by flank sucking repetitively suck, lick or chew the hair or skin on their flanks, causing skin irritation.

Behavior Modification Tips

Behavior modification, combined with drug therapy, can alleviate blanket and flank sucking disorders in some Doberman Pinschers. Here are behavior modification tips.

- Avoid stress triggers that lead to sucking behavior
- Do not punish or reinforce compulsive behavior
- Be sure a dog exercises vigorously 20 to 30 minutes a day
- Maintain a consistent schedule for feeding, walking, playing, and sleeping
- Practice obedience training to introduce new commands, stimulate learning and decrease stress
- Provide an enriched environment with chew toys and interactive feeders
- Introduce sports such as agility and rally obedience to add variety
- Interrupt compulsive behavior using counter-conditioning techniques such as giving specific commands and redirecting the dog’s attention to other activities

Canine Mammary Cancer Study Modeled After Advances in Human Stem-Cell Research

Mammary cancer is as familiar to dog breeders and owners as breast cancer is to people whose loved ones have been diagnosed with the devastating disease. Research of human mammary stem cells provides a model for research in dogs that may help advance the use of drugs to inhibit the growth potential of cancer cells.

A study underway at the Baker Institute for Animal Health at Cornell University is evaluating the role of citrullination, a cellular process mediated by peptidylarginine deminase (PAD) enzymes, in canine mammary cancer. PAD activity, which is usually low in healthy tissues, often increases during mammary cancer development, says lead investigator Gerlinde Van de Walle, DVM, PhD, assistant professor.

The collaborative study, which is
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hair loss and raw, open sores. Dobermans that suck or chew on blankets could develop lip calluses or digestive problems if they chew and swallow fabric, a condition known as pica.

“Blanket sucking and ingestion of inedible objects appear to occur on a continuum,” Dodman says. “Dogs begin sucking and then progress to chewing and ingestion as an extension of the same behavior. Pica may require emergency surgery to remove obstructions from the throat or intestines of affected dogs.

“If owners take away the blanket, an affected Doberman usually finds another object. Similarly, dogs disciplined for flank sucking often simply hide away to engage in the behavior rather than discontinue it. These behaviors provide relief from anxiety, but the anxiety quickly returns and leads to more of the same behavior. It becomes a vicious cycle.”

An Anatomical Blueprint for CCD

A study showing insights about the differences in the brains of affected and unaffected Doberman Pinschers came from sophisticated brain scans, performed in cooperation with the McLean Imaging Center in Belmont, Massachusetts, which is affiliated with Harvard Medical School. Eight dogs with flank or blanket sucking behaviors and eight unaffected dogs were included in the study.

“We found an anatomical blueprint for canine compulsive disorder,” Dodman says. “The structural changes in the brain were significantly different, and those changes were almost the mirror image of changes in people with hoarding disorder. Not surprisingly, many dogs that suck blankets and flanks also compulsively collect objects.”

Likewise, the first mutation discovery in the neural cadherin-2 gene relates to the role of cadherins in humans and their association with autism spectrum compulsive disorders. “It’s a huge coincidence that first we find the CDH2 gene on chromosome 7 that activates a pathway in the brain responsible for the formation of receptors blocking nervous system communication, and now we find modifier genes connected to the serotonin system,” says Dodman. “We believe the serotonin genes are responsible for modifying the severity of the condition.”

Research has shown that blanket and flank sucking are related to nursing and eating behaviors. Some Doberman Pinschers exhibit only one behavior, and others develop both. “The onset of flank and blanket sucking occurs most commonly before sexual maturity, and the behaviors may be precipitated by anxiety or stress,” Dodman says. “The behavior soon becomes fixed and then occurs in the absence of obvious stressors.”

The compulsive behaviors are believed to originate from an insatiate suckling drive. Early weaning may aggravate the tendency for both sucking disorders. Later weaning after 12 weeks seems to protect Oriental cat breeds that suffer from pica, in which they suck, lick, chew, and swallow objects such as wool, paper and plastic, Dodman says.

Canine compulsive disorders usually require lifelong medical management combined with behavior modification. Medical management using selective serotonin reuptake inhibitors (SSRIs) prescribed alone or in combination with N-methyl-D-aspartate (NMDA) receptor antagonists has proved to be effective.

An SSRI medication, fluoxetine, helps to increase serotonin levels in the brain. SSRIs are most commonly used to help treat depression in people by blocking the reabsorption or reuptake of the neuro-
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transmitter serotonin in the brain. An NMDA receptor antagonist, memantine, a drug used to treat Alzheimer’s disease in people, helps block the functioning of glutamate, a brain chemical necessary for nervous system communication, memory and learning.

“We know you can increase serotonin and block NMDA receptors and glutamate to control compulsive disorders,” Dodman says. “When memantine is combined with fluoxetine, the effects are synergistic because lower doses of both drugs together produce a better reaction. SSRIs can help some dogs, but that alone is not a panacea.”

A Tufts study published in the Journal of Veterinary Behavior in 2009 showed the results of medicating 11 dogs affected with CCD with memantine. The treatment was effective and well-tolerated in many of the treated dogs.

“These disorders are best treated with a combination of medication and behavior modification therapy,” Dodman says. “Owners should adjust an affected dog’s environment to remove stress triggers and be sure the dog gets plenty of exercise and has an enriched lifestyle. It also is important to feed a complete and balanced diet. In some cases, canine compulsive disorders can be completely controlled.”

Despite the challenges of dealing with blanket or flank sucking tendencies, it is good to know that with proper management an affected Doberman Pinscher can usually live a normal life. Meanwhile, genetic research to learn more about what causes CCD may one day lead to better understanding that will provide effective treatments and benefit breeding decisions.

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funded by the Morris Animal Foundation, includes Scott Coonrod, PhD, the Judy Wilpon associate professor of cancer biology at Cornell University Laboratory of Epigenetics and Cancer Biology. His research in human breast cancer cell lines provides the basis for the canine study.

“We are basically studying whether the cancer stem-cell lines in dogs, as in people, express higher levels of PAD enzymes and whether drugs that inhibit the function of these enzymes can reduce the tumorigenicity of these cancer cells,” Van de Walle says.

“Mammary stem cells are a small population of cells present in the mammary gland, yet they are the driving force behind regeneration of the gland. These cells remain in the tissue for a long time, thus there is a greater chance of them becoming tumors when compared to normal adult cells that die and are replaced by new cells.”

In his work in human breast cancer, Coonrod showed that the binding of estrogen to the estrogen receptor appears to attract PAD2 enzymes to genes that promote tumor growth. As a result, the PAD2 enzymes citrullinate genes that increase transcriptional activity and promote expression of proteins involved in tumor progression.

Citrullination is a process in which positively charged arginine residues are changed to neutral citrulline residues, thus changing the charge of proteins.

“This process changes a protein’s three-dimensional structure and affects how it interacts with other proteins on other cells,” Van de Walle says. “PAD enzymes catalyze the conversion of protein-bound arginine to citrulline.”

PAD inhibitors are drugs that inhibit PAD enzymes and thus may have an anti-tumor effect. “Our preliminary studies indicate that PAD inhibitors reduce the tumorigenic potential of canine mammary cancer cells, and they also do not harm healthy mammary cells. We are working on determining the relation between PAD inhibitors and PAD expression and function in dogs with mammary cancer.”

The goal is to study the efficacy of PAD inhibitors in a clinical trial of dogs with mammary cancer. “Before we can evaluate these drugs in dogs with mammary tumors, we need to be sure the drugs are safe at a therapeutic dose,” says Van de Walle.

The future holds promise that PAD inhibitors may one day provide an effective treatment for canine mammary cancer. In the meantime, owners should be diligent about checking their dogs for signs of cancer before it spreads. The earlier a mass is found and surgery is performed to remove it, the better chance there is for a successful outcome.

Did You Know?

- Mammary cancer is the most common tumor in intact female dogs
- Although rare, mammary cancer also can occur in male dogs
- Spaying before the first estrous cycle (around 6 months of age) reduces the risk of mammary cancer to 0.5 percent
- Early recognition of signs of mammary cancer offers hope that treatment may provide a cure. These include large, firm lumps and swelling in mammary tissue, lack of appetite, weight loss, and general weakness
‘Matisse’ Wins Pro Plan Champions Cup

After leading the pack all year, GCH Claircreek Impression De Matisse has won the 2014 Pro Plan Champions Cup by earning 480 points through Dec. 31. The 3 ½-year-old male Portuguese Water Dog, called “Matisse,” was bred by Donna Gottdenker, who co-owns him with Milan Lint and Peggy Helming. Professional handler Michael Scott handles Matisse, who finished second in the 2013 Champions Cup competition.

The yearlong Pro Plan Champions Cup award, which is sponsored by Purina Pro Plan brand dog food, is based on points tabulated from Bests in Show and Group placements at more than 200 Purina-sponsored all-breed dog shows. The winner receives a $10,000 cash prize, an original oil painting by dog portrait artist Linda Draper and a keepsake Pro Plan Champions Cup trophy.

Take a look and see if you recognize the Top 10 placing dogs.

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