

TWO NEW DNA BASED TESTS AVAILABLE FOR THE NSDTR

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We are very excited to report two new DNA based tests available for the NSDTR, one for juvenile onset Addison's disease (*JADD*) and one for one form of cleft palate (*CPT1*). The tests are available through the Orthopedic Foundation for Animals. Test kits (swab-based) will be ordered through OFA and the test results will be automatically included in the OFA database. Both of these tests are being offered to breeders prior to peer reviewed scientific publication in order to allow their immediate use in breeding programs. In both cases additional research is being conducted and when it is completed the information about the specific genes involved will be made available.

We are also continuing to work on both Addison's disease and cleft palate in the NSDTR and want to strongly encourage breeders to continue sending samples. This will enable the identification of the additional cleft palate genes as well as help us clarify the nature of the *JADD* mutation. Email contact information for cleft palate is ztwolf@ucdavis.edu and for Addison's disease it is dlbannasch@ucdavis.edu

The research on Addison's disease was funded by the Center for Companion Animal Health, University of California-Davis and the AKC Canine Health Foundation Acorn grant. The research on cleft palate was funded by the Center for Companion Animal Health, University of California-Davis, AKC Canine Health Foundation Oak grant, and the Lady Grey Foundation.

We would like to thank the Tollers owners and breeders world-wide for submitting samples and veterinary information about their dogs. Without their contributions these tests would not have been possible.

Juvenile Addison's disease (*JADD*) in the Nova Scotia Duck Tolling Retriever (NSDTR)

Addison's disease (hypoadrenocorticism) occurs when the adrenal glands stop secreting the natural steroid hormones (glucocorticoid) and hormones (mineralocorticoids) necessary for the regulation of sodium and potassium levels in the blood. Addison's disease can occur in any breed of dog and it has an average age of onset of 4 years. Addison's disease is diagnosed by a veterinarian using a blood test called an ACTH stimulation test. The clinical signs of Addison's disease can include lethargy, inappetance, vomiting and diarrhea.

In the NSDTR, a genetic form of this disease, called *JADD*, occurs in much younger animals. The average age of puppies affected with *JADD* is 5 months; however, puppies as young as 8 weeks and as old as 12 months of age have been identified.

Treatment of puppies affected with *JADD* requires both mineralocorticoid and glucocorticoid replacement therapy. Puppies can have other concurrent diseases including eye problems (corneal edema, conjunctivitis or uveitis) that may require specialized treatment.

Discovery:

Scientists from the Bannasch Laboratory at the University of California, Davis have developed a DNA test to identify carriers of *JADD* in the Nova Scotia Duck Tolling Retriever. The juvenile form of Addison's disease is genetically distinguishable from the adult onset form in that all dogs developing the juvenile form have two identical copies of a specific region within their genome. Our lab has identified numerous markers within this region and we have compiled these markers into a haplotype based test in order to identify dogs that carry *JADD*. We believe that in addition to the markers that distinguish affected puppies from unaffected ones, the actual mutation responsible for *JADD* is included in this haplotype test.

The mutation responsible for *JADD* causes a change in the amino acid sequence in a highly conserved region of a protein. This mutation is not present in any other breeds of dogs based on testing of over 250 individual animals in 80 different breeds. However, additional research is needed to demonstrate how this mutation causes *JADD* in Tollers. We offer the test now to help breeders avoid producing affected puppies while we continue to understand the mechanism of the mutation. Please contact researchers if you have an affected puppy and would like to participate in the project (dlbannasch@ucdavis.edu).

The mode of inheritance:

This form of the disease is inherited as an autosomal recessive disease meaning that affected puppies inherited one mutant copy of this gene from each of their parents. In addition, *JADD* is not completely penetrant meaning that not all puppies with two copies of the mutation will go on to develop the disease. Based upon our research, approximately 75% of puppies with two copies of the mutation and haplotype will develop Addison's disease.

The test:

<i>JADD Probable N/N</i>	This dog has two normal copies of the <i>JADD</i> region
<i>JADD Probable N/A</i>	This dog has one mutant (abnormal) copy of the <i>JADD</i> region
<i>JADD Probable A/A</i>	This dog has two mutant (abnormal) copies of the <i>JADD</i> region and has a 75% chance of developing Addison's disease by 1 year of age.

In order to keep the costs of this test low it will be run in batches of 48 samples which could affect the turnaround time for results.

Counseling:

JADD is inherited as an autosomal recessive disease meaning that animals have only one mutant copy of the region (N/A) are normal but they are carriers of the disease and they can produce affected puppies if bred to an affected dog (A/A) or another carrier (N/A). At the time that this test was released approximately 20% of Tollers carry *JADD* (N/A); however, the number of carriers can change with each generation. Dogs that are carriers (N/A) are normal themselves and can be safely bred to N/N dogs in order to maintain diversity within the breed and select for other positive attributes in carrier dogs. If you have a dog identified as being A/A or having early onset Addison's disease (<1 year old) and you would like to participate in further research to understand this disease please contact Danika Bannasch DVM PhD, dlbannasch@ucdavis.edu.

JADD Key points:

This is a haplotype test which includes the probable mutation as well as informative markers across the region therefore the status of a dog is reported as probable.

This disease is autosomal recessive with 75% penetrance. Meaning that 75% of dogs with two copies of the mutation will get Addison's disease, the other 25% will not.

Neither the decreased penetrance nor the "probable" designation precludes using clear by parentage for litters of puppies born of parents tested to be clear.

Adult onset Addison's is a separate disease. JADD is characterized by Addison's disease occurring under 1 year of age and possible other autoimmune problems. Based on the clinical histories of 20 dogs affected with JADD, those with Addison's disease had both mineralocorticoid and glucocorticoid deficiency by 12 months of age. Most had eye problems and some had other autoimmune diseases.

Comparison of age (in months) in JADD and NON-JADD cases

	Average	Median	Youngest	Oldest
JADD (20 dogs)	5.3	4	2	12
NON-JADD (17 dogs)	52.5	60	6	120

In making testing decisions, one should not assume that a historical case of Addison's was JADD or not based on age of onset of the disease.

We are continuing to work on this disease and will be grateful for information and samples from affected dogs.

Cleft Palate (CP1) in the Nova Scotia Duck Tolling Retriever (NSDTR)

A cleft palate is a birth defect whereby a hole (cleft) in the roof of the mouth (palate) develops in a puppy during gestation. Puppies born with cleft palate can experience difficulty nursing which will greatly increase their risk of developing aspiration pneumonia - a serious life threatening condition. There are **multiple genetic causes of cleft palate** within the NSDTR breed; however, the most common form has been identified as *CP1*.

The mutation test we have developed identifies carriers of CP1 within the NSDTR breed. It does not apply to any breed other than the NSDTR. If you have a puppy of a different breed with cleft palate and you wish to participate in the identification of the gene(s) responsible please contact the Bannasch Laboratory at the University of California at Davis (ztwolf@ucdavis.edu).

Discovery:

Scientists from the Bannasch Laboratory at the University of California, Davis have discovered the genetic cause of **ONE FORM** of cleft palate in the Nova Scotia Duck Tolling Retriever. Dogs with this form of cleft palate have a large insertion into a gene known to affect the proper development of the palate. This mutation is not present in any other breed based on testing conducted on over 300 individual animals of over 80 different dog breeds.

The mode of inheritance:

Cleft palate caused by *CP1* is a simple autosomal recessive disease meaning that an affected puppy has inherited one mutant copy of the gene from each parent.

The test:

<i>CP1 N/N</i>	This dog has two normal copies of <i>CP1</i>
<i>CP1 N/A</i>	This dog has one mutant (abnormal) copy of <i>CP1</i>
<i>CP1 A/A</i>	This dog has two mutant (abnormal) copies of <i>CP1</i>

In order to keep the cost of this test low the test will be run in batches of 48 which could affect the turnaround time for results.

Counseling:

CP1 is an inherited autosomal recessive disease. Animals that have only one mutant copy of *CP1* (*N/A*) are normal but they are carriers of the disease. When two carriers are bred to each other the resulting puppies can be affected. At the time that this test was released, approximately 15% of Tollers were carriers of *CP1* (*N/A*); however, the number of carriers can change with each generation.

To date we have received 29 samples from North American NSDTR puppies with cleft palate, 18 of which had two mutant (*CP1 A/A*) copies of *CP1*. Dogs that are carriers of *CP1* (*N/A*) are completely normal and they can be safely bred to dogs that are non carriers of *CP1* (*N/N*) in order to maintain diversity within the breed and to select for other positive attributes in carrier dogs. Puppies affected with cleft palate will be tested at no charge. Please contact Zena Wolf for more details (ztwolf@ucdavis.edu).

CP1 Key points:

There are more genetic causes of cleft palate in the breed than just CP1. We are actively working on identifying the other causes and will test puppies with cleft palates at no charge. This means that just because a puppy has a cleft does not mean it is caused by CP1 and that just because a dog is clear does not mean that it can't produce clefts from other genetic causes.

In making testing decisions one should not presume that a puppy born with a cleft had the CP1 mutation.

CP1 is inherited as a simple autosomal recessive.

There are now five DNA tests available for the NSDTR. In addition to DNA based tests, CERF exams and hip evaluations are recommended for all breeding Tollers (CHIC). Many breeders also perform heart, patella, thyroid and elbow evaluations prior to breeding. The following table was created based on the most current data from the scientific literature and the testing company web sites in order to facilitate breeder decisions regarding DNA based tests.

Current disease related DNA tests for the NSDTR counseling information

Disease	Test Type	Inheritance	Penetrance NSDTR	Penetrance Other	Treatment	Life Expectancy	Age of onset	Carrier rate
prcd	Mutation	Recessive	<100%	<100%	None	Normal	4 yrs-never	40%***
CEA	Mutation	Recessive	?	5-8%*	None	Normal	Birth	5%***
DM	Mutation	Risk	?	Age related	None	Reduced	8-14 years	?
JADD	Haplotype	Recessive	75%	N/A	~\$200/month	3.75 yrs	8 wks-1 yr	20%
CP1	Mutation	Recessive	100%	N/A	Surgery**	Unknown	Birth	15%

*Vision abnormalities

**If puppy is tube fed and survives the neonatal period, the cleft can be surgically repaired

***Optigen Website

Abbreviations:

N/A Not Applicable

N/A Not Applicable

Prcd- progressive retinal atrophy

CEA- Collie Eye Anomaly

DM- Degenerative Myelopathy

JADD-Juvenile Addison's disease

CP1- Cleft Palate 1

Degenerative Myelopathy for NSDTR fits into the category of "other breeds". For further information:

<http://www.offa.org/dnatesting/dm.html>

"Clear by parentage" would be appropriate for any of the DNA tests. Since all tests are for recessive or recessive risk mutations, if both the parents are tested "clear" or "normal" then the offspring from that cross will also all be "clear" or "normal". The OFA currently offers this designation for one generation.