

Exercise Induced Collapse in Labrador Retrievers and Related Breeds

The Syndrome of EIC

Recent research at the University of Minnesota has identified the gene responsible for the condition known as exercise-induced collapse (EIC). EIC is a recently recognized disorder of increasing significance in Labrador Retrievers, especially those dogs used for hunting and field trials. Dogs affected with EIC develop muscle weakness, incoordination and life-threatening collapse after just five to fifteen minutes of field exercise and cannot participate in many types of strenuous activities. The condition also exists undetected in Labradors that are not routinely participating in such activity.

Our research into the genetic basis of EIC has identified a mutation in the canine dynamin 1 (DNM1) gene, which is very likely to be fundamentally responsible for EIC. The dynamin 1 protein encoded by the DNM1 gene functions to maintain neural and neuromuscular transmission during high intensity stimulation. Thus, a DNM1 mutation that affects the function of the dynamin 1 protein could logically explain the physical and downstream clinical signs associated with EIC episodes.

Research performed by Dr. Sue Taylor and colleagues at the University of Saskatchewan is responsible for most of our knowledge concerning the clinical and physiological characteristics of EIC, as well as criteria for diagnosis, medical issues, and evaluation of various therapies. This information is available in more detail in the following document.

www.vdl.umn.edu/vdl/ourservices/canineneuromuscular/taylor2008

Finding the EIC Gene

With the assistance of many hundreds of veterinarians and owners we were able to collect sufficient samples from well-defined EIC cases and normal controls to perform a genetic study to identify the EIC gene. We first identified the precise chromosomal location of the EIC gene during a “genome scan” with “DNA markers”. In this genome scan DNA markers that are present at known and unique locations on each of the dog chromosomes were used to identify specific patterns of inheritance of these chromosomal segments in DNA samples from hundreds of dogs. An examination of the inheritance pattern of these DNA markers in multi-generation Labrador Retriever pedigrees where EIC was present, eventually identified a small segment on canine chromosome 9 that must contain the EIC gene.

We then sequenced the DNA of several candidate genes in this small chromosomal region that are involved in muscle and nerve metabolism and function. Several genes were ruled out but a DNA sequence difference (i.e., a mutation) between EIC and control dogs in the DNM1 gene was identified. This is a compelling candidate causal mutation for EIC due to the critical role of the protein encoded by this “EIC gene” in synaptic communication between nerves in the central nervous system and between nerve and muscle at the neuromuscular junction.

A manuscript reporting these exciting results was published in the October 2008 issue of Nature Genetics, one of the most highly regarded journals of genetic research. The article can be found under the following citation: Patterson EE, Minor KM, Tchernatynskaia AV, Taylor

SM, Shelton GD, and Mickelson JR. (2008). A canine dynamin 1 (*DNM1*) mutation is highly associated with the syndrome of exercise-induced collapse. *Nature Genetics* 40, 1235-1239.

The discovery of the EIC gene and its mutation will provide breeders and veterinarians with a non-invasive test for diagnosis, and a selection method for designing matings that can limit the production of affected dogs.

The Genetics of EIC

EIC appears to be a genetically simple trait that is due to a mutation in just one of the approximately 20,000 genes present in a dog's genome. We have designated the letter E to indicate the mutant form or EIC form of the *DNM1* gene and N to indicate the normal form of this gene. Every dog has two copies of the *DNM1* gene, one inherited from the dam and one inherited from the sire. Every dog inherits either the N or the E form of the *DNM1* gene from each parent. In other words, a mutation in the *DNM1* gene produces the E form of the gene, which may sometimes be referred to as the EIC gene.

A dog's particular combination of E or N forms of the *DNM1* gene is known as its genotype. Thus far our genetic testing has identified more than 400 dogs greater than three years of age with the E/E genotype. Analysis of available descriptions of these dogs shows that more than 80% of them have the classical signs of EIC, and have had at least one, but usually multiple well-documented collapse episodes. Such dogs may be referred to as homozygotes for the EIC mutation.

The genotype of a dog that is clear of the EIC mutation is designated as N/N, while E/N dogs are referred to as carriers or heterozygotes. Our testing to date has identified more than 1,000 dogs with the E/N genotype. Approximately 96% of these dogs have no signs of EIC or any type of collapse, while approximately 4% have been reported to show some signs of collapse or intolerance associated with exercise. The vast majority of these collapses can be attributed to other medical conditions, or their signs are not consistent with the classic signs of EIC that starts with wobbliness in the rear legs.

Similarly, approximately 5% of all dogs with the N/N genotype are reported by owners to show some signs of an exercise-associated weakness or collapse that is likely due to other causes and is not classic EIC. Thus, we feel there is sufficient evidence to state that carriers of the EIC gene are not more likely to show signs of a collapse than are clear dogs, and that any collapse symptoms they are very likely to be EIC.

All parents of dogs with EIC that we have tested so far are either E/N or E/E. This means that the parents are either unaffected carriers of the mutant EIC gene, or they are homozygous for the mutant *DNM1* gene and therefore genetically susceptible to EIC themselves.

The genetic term that best describes the research data gathered to date is that EIC is inherited in an autosomal recessive fashion, because two copies of the mutant form of the *DNM1* gene (i.e., the E/E genotype) are required for a dog to be affected, and an affected dog gets an E form of the *DNM1* gene from each parent.

The most accepted way for scientists to describe this situation is to state that the DNM1 mutation is highly associated with EIC. Scientists are always cautious and do not state their conclusions with 100% certainty. However, the chances that the DNM1 mutation is not associated with EIC are less than 1 in a trillion as reported in our Nature Genetics article. This situation is different from other types of genetic tests that describe only the identification of a marker with no known gene or mutation as the almost certain cause. The role of DNM1 in nerve and muscle function clearly supports it being an extremely plausible EIC gene. A description of the precise effect of the DNM1 mutation on the function of the dynamin 1 protein remains before we can even more confidently state that the DNM1 mutation (i.e., E form of the this gene) is the causative EIC mutation.

Implications of the EIC Mutation for Breeding

Breeding two clear dogs

		Sire's Genotype	
		N	N
Dam's Genotype	N	N/N	N/N
	N	N/N	N/N

Breeding a clear dog to an affected dog

		Sire's Genotype	
		N	N
Dam's Genotype	E	N/E	N/E
	E	N/E	N/E

Breeding a clear dog to a carrier dog

		Sire's Genotype	
		N	N
Dam's Genotype	N	N/N	N/N
	E	N/E	N/E

Breeding a carrier dog to an affected dog

		Sire's Genotype	
		N	E
Dam's Genotype	E	N/E	E/E
	E	N/E	E/E

Breeding two carrier dogs

		Sire's Genotype	
		N	E
Dam's Genotype	N	N/N	N/E
	E	N/E	E/E

Breeding two affected dogs

		Sire's Genotype	
		E	E
Dam's Genotype	E	E/E	E/E
	E	E/E	E/E

One way to present the probability that puppies with EIC will be produced from the mating of parents of each of the three possible genotypes is shown above. Each parent, depending on its genotype, will contribute either the E or the N form of the EIC gene to a puppy. This in turn will result in that particular puppy's own genotype of N/N, E/N, or E/E. Each of the four

squares shown for each of the six possible matings in the Figure represents a 25% chance for producing a pup with that genotype. Thus, the matings resulting in one, two or four red squares will on average produce litters containing 25%, 50% and 100% EIC affected pups, respectively.

For example, breeding an E/N sire to an N/N dam can only produce puppies that are E/N or N/N, and according to our current data that supports a recessive mode of inheritance, none would be susceptible to EIC (2 blue squares and 2 purple squares). On the other hand, breeding an E/N sire to an E/E dam gives a 50% chance that a puppy will have EIC, since puppies can be either E/N or E/E (2 purple squares and 2 red squares). All puppies from the mating of two E/E parents will be E/E and thus likely be susceptible to EIC (four red squares). Mating an E/E parent to a clear N/N parent would not produce affected puppies (4 purple squares), but all would be carriers.

Lastly, and very importantly, we do not recommend selecting dogs for breeding based solely on their both being N/N for the DNM1 gene. Such a drastic strategy, although more quickly eliminating the possibility of producing E/E genotypes and EIC affected dogs, also has the undesired result of losing many of the outstanding exercise and performance traits expected of many lines of Labrador Retrievers. A better approach would enable the continued use of some of the many excellent E/N and E/E dogs by mating them to N/N dogs. This would produce litters without EIC and a choice of dogs to progressively decrease the frequency of the E form of the DNM1 gene by future matings to N/N dogs.

Contact for questions

For additional questions concerning EIC please email us at: eicinfo@umn.edu