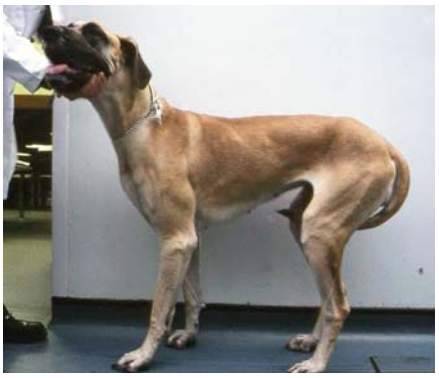
June 6th, 2013

A new model of centronuclear myopathy in Great Danes



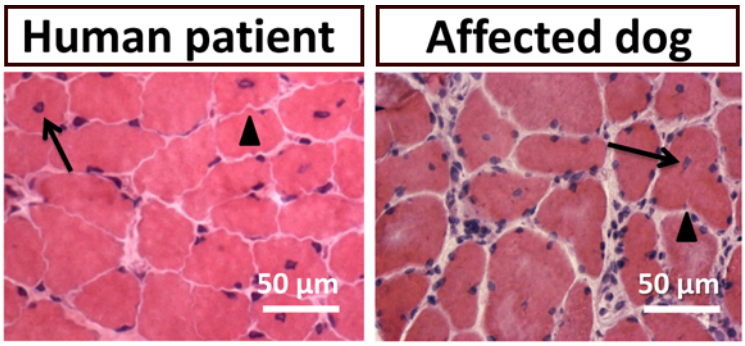
Altered Splicing of the BIN1 Muscle-Specific Exon in Humans and Dogs with Highly Progressive Centronuclear Myopathy. Böhm J, Vasli N, Maurer M, Cowling B, Shelton GD, Kress W, Toussaint A, Prokic I, Schara U, Anderson TJ, Weis J, Tiret L, Laporte J.
PLoS Genet. 2013 Jun;9(6):e1003430.

History of the disease

Few years ago, cases of inherited myopathy in Great Danes living in Canada and Australia have been reported by two independent scientific groups[1]. These initial cases were described as "Central core myopathy" or "Inherited Myopathy of Great Danes" and movies of affected dogs can be seen on www.centralcoremyopathy.info/video.htm.

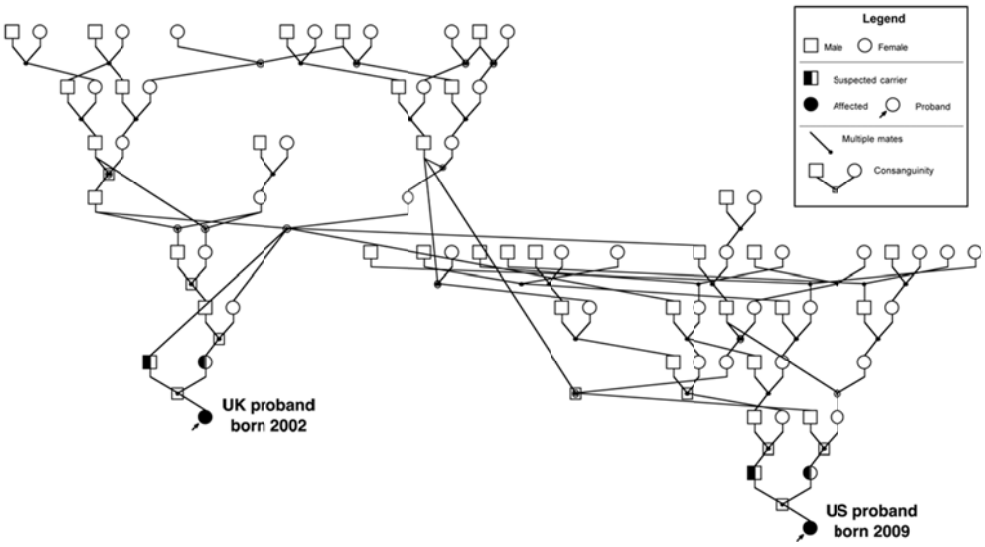
Histopathological and molecular characterization of the disease

More recently, additional cases have been diagnosed in the USA and in-depth evaluation of muscle biopsies revealed that this autosomal recessive disorder has indeed histological features of centronuclear myopathy (CNM), and more precisely of a highly progressive human forms of CNM that remained unresolved at the molecular level. Common histopathological features between human and canine forms are displayed on the following figure, with centralized nuclei (arrows) and membrane defects (arrow heads).



Our scientific work then consisted in identifying the genetic mutation causing CNM in Great Danes. A mutation in the *BIN1* gene, previously implicated in autosomal recessive centronuclear myopathy in human[2], was found to be the cause of this canine myopathy.

In dogs, careful analyses of pedigrees including affected dogs (probands, see an example below, excerpted from the manuscript) allowed to postulate that a unique mutation accounts for all cases of this specific inherited myopathy described recently in the USA and previously in the UK, Canada and Australia.



A direct consequence of this molecular characterization is the development of a genetic test for CNM in Great Danes, meaning that owners now have the possibility to confirm at the DNA level which of disabled dogs are indeed affected by this form of CNM as previously performed in Labrador retrievers[3] (www.labradorcnm.com), to avoid matings at risk in the future, and to identify carrier for the establishment of a colony for research use.

Importantly, a similar mutation of the same *BIN1* gene was also found in human patients, with highly similar muscle alterations and phenotypes. This canine model impressively mimics a highly progressive autosomal recessive form of centronuclear myopathy in humans.

[1] McMillan CJ, Taylor SM, Shelton GD. Inherited myopathy in a young Great Dane. Can Vet J. 2006 Sep;47(9):891-3; Davies SE, Davies DR, Richards RB, Bruce WJ. Inherited myopathy in a Great Dane. Aust Vet J. 2008 Jan-Feb;86(1-2):43-5.

[2] Nicot AS, Toussaint A, Tosch V, Kretz C, Wallgren-Pettersson C, Iwarsson E, Kingston H, Garnier JM, Biancalana V, Oldfors A, Mandel JL, Laporte J. Mutations in amphiphysin 2 (BIN1) disrupt interaction with dynamin 2 and cause autosomal recessive centronuclear myopathy. Nat Genet. 2007 Sep;39(9):1134-9.

[3] Maurer M, Mary J, Guillaud L, Fender M, Pelé M, Bilzer T, Olby N, Penderis J, Shelton GD, Panthier JJ, Thibaud JL, Barthélémy I, Aubin-Houzelstein G, Blot S, Hitte C, Tiret L. Centronuclear myopathy in Labrador retrievers: a recent founder mutation in the PTPLA gene has rapidly disseminated worldwide. PLoS One. 2012;7(10):e46408.

Dr Jocelyn Laporte
IGBMC
France
http://igbmc.fr/Laporte

Dr G. Diane Shelton
University of California
The USA
http://vetneuromuscular.ucsd.edu/

Dr Laurent Tiret
ENVA
France
http://genetics.vet-alfort.fr
http://www.labradorcnm.com