



Happy Holidays



from the Beggs' Congenital Myopathy Research Program
at Children's Hospital Boston & Harvard Medical School

2009 was another exciting year in the Beggs laboratory, as we continued to gain a better understanding of the role of selenoprotein N, nebulin and myotubularin in normal muscle function and disease. Our mouse models of MmD, NM, and XLMTM are now well-established, helping us to illuminate the cause and symptoms of each disease and consider potential treatments. Through the use of zebrafish, we have identified several potential candidate genes for congenital myopathies, and we are now trying to clarify their role in human muscle disease. In 2010, our team will continue to work towards our goal of identifying and understanding genes involved in the congenital myopathies, in the hopes of allowing for better diagnosis and treatment for families in the future. Our work would not be possible without the generous participation and support of families and colleagues like you.

Thank you for your support & Happy New Year!



PARTICIPATION & MORE

We are enrolling patients and their families into our studies on congenital myopathies, including centronuclear myopathy (CNM)/ X-linked myotubular myopathy (XLMTM), congenital fiber type disproportion (CFTD), multiminicore disease (MmD), nemaline myopathy (NM) and undefined congenital myopathies. For more information about our research and the topics in this newsletter, to request to be removed from the mailing list, or to inquire about making a donation, please visit our website at www.childrenshospital.org/research/beggs or contact our research coordinator:

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IMPROVING OUR UNDERSTANDING OF MMD AND NM

In addition to the mice with XLMTM that we have been studying, our laboratory has now established mouse models of multiminicore (MmD) and nemaline myopathies (NM), helping us to understand each disease's symptoms and effects on muscle function. Dr. Behzad Moghadaszadeh and his team have developed mice with a mutation of the *SEPN1* gene, also called a "SEPN1 knock-out," to better understand the role that this gene plays in muscle function. Remarkably, these mice initially appear healthy, but by changing their diet to increase cellular stress, Behzad is able to induce the formation of minicores, just like the ones seen in humans with MmD. Similar to humans, the *SEPN1* knock-out mice develop respiratory issues as they age. The team is now working to better understand the specific symptoms in the mice, when they occur, and what causes them. Pankaj Agrawal, MD and his team are studying mice with non-working cofilin-2 ("CFL2, knock-out"), which is one of the genes associated with NM and minicores. The *CFL2* knock-out causes the mice to have severe weakness and muscle changes similar to those seen in humans with *CFL2* mutation. By varying when in development and/or where in the body the *CFL2* mutation is expressed, we are learning more about the specific role cofilin-2 plays in muscle function and when in development it is important. Studying these mouse models of MmD and NM is leading us to new ideas for possible treatments, which we will be able to safely test in the mice in preparation for eventual human clinical trials.

IDENTIFYING A DOG WITH MTM

Recently, Drs. Elizabeth Snead and Diane Shelton identified several Labrador retrievers with weakness and an unknown myopathy. These dogs have comparable symptoms and similar-appearing muscle to boys with X-linked myotubular myopathy (XLMTM). We have now confirmed that these dogs do in fact have XLMTM, as Marek Kozlowski, MS helped identify a genetic mutation in the dogs' *MTM1* gene that is believed to cause their disease. For more details about the story of identifying these dogs, visit www.joshuafrase.org/info/nibs.php.

RESOURCES FOR PATIENTS

General Resources:

Muscular Dystrophy Association (www.mdausa.org)

Genereviews (www.genereviews.org)

Connections to Families:

Facebook Groups at www.Facebook.com

-Search NM Global Awareness, Centronuclear, Myotubular, or Nemaline

Yahoo Groups at groups.yahoo.com

-Search CFTDmail, Minicore, Myopathy, Myotubular, Nemaline

Condition Specific Resources:

CFTD:

The Caytton Wheeler Foundation (www.cayttonwheeler.org)

CNM/MTM:

The Frase Foundation (www.joshuafrase.org)

The Info Point for CNM/MTM (www.centronuclear.org.uk)

MTM Resource Group (www.mtmrg.org)

NM:

The NM Support Group (www.nemaline.org)

The NM Foundation (www.nemalinefoundation.org)

A Foundation Building Strength for NM

(www.buildingstrength.org)

CLINICAL GENETIC TESTING

Clinical genetic testing is now available for many of the genes associated with the congenital myopathies. More information is available at www.genetests.org.

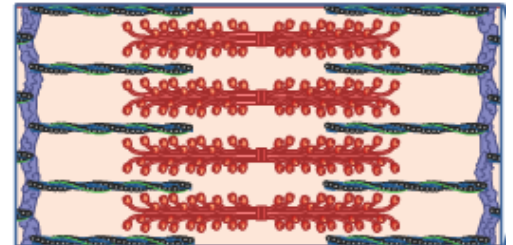
DISEASE	ASSOCIATED GENES			
	(% of cases with mutations in given gene)			
CFTD	TPM3 (20-30%)	ACTA1 (6%)	SEPN1 (rare)	
CNM	DNM2 (?)	RYR1 (?)		
XLMTM	MTM1 (>80%)			
MmD	SEPN1 (30-50%)	RYR1 (?)		
NM	ACTA1 (15-25%)	TPM2/ TPM3 (<10%)	NEB (~50%)*	TNNT1 (rare)
RSMD**	SEPN1 (?)			

* Full sequencing and specific testing for the exon 55 deletion, a mutation more common in the Ashkenazi Jewish population, are both available.

** Rigid spine muscular dystrophy

THE GENES INVOLVED IN NEMALINE MYOPATHY

The six genes associated with nemaline myopathy all help form part of the muscle "sarcomere" (pictured below), which allows muscle to contract. Nebulin acts as a scaffold for a structure called the "thin filament," to which the other five NM gene products (*ACTA1*, *TPM3*, *TPM2*, *TNNT1*, and *CFL2*) attach. Through a collaboration with Drs. Henk Granzier and Coen Ottenheijm of the University of Arizona and VU University Medical Center in Amsterdam, we are working to better understand the specific effect of mutations in each of these NM genes. By teasing apart individual muscle fibers from patient muscle biopsies we can study how the individual filaments work. Within healthy muscle, cross bridges form between different parts of the contractile mechanism (like two people grabbing hands), allowing the parts to pull past each other, resulting in a force that produces muscle contraction or shortening. Coen has found that muscle fibers of patients with nebulin gene (*NEB*) mutations contain significantly less nebulin, and the muscle is less sensitive to calcium, which plays an important role in promoting contraction. These studies suggest that patients with abnormal nebulin are unable to form as many cross bridges, resulting in producing less force and therefore weaker muscle contraction. We are now analyzing the muscle of patients with alterations in other NM genes to see how they differ. To view an animation of muscle contraction and the effects of alterations in different NM genes, visit www.childrenshospital.org/research/beggs/nemaline



RECENT PUBLICATIONS AND EVENTS

Al-Qusairi L, Weiss N, Toussaint A, Berbey C, Messaddeq N, Kretz C, Sanoudou D, Beggs AH, Allard B, Mandel JL, Laporte J, Jacquemond V, Buj-Bello A. T-tubule disorganization and defective excitation-contraction coupling in muscle fibers lacking myotubularin lipid phosphatase. *Proc Natl Acad Sci U S A*. 2009;106(44):18763-8.

Lawlor MW, Dechene ET, Roumm E, Geggel AS, Moghadaszadeh B, Beggs AH. Mutations of tropomyosin 3 (TPM3) are common and associated with type 1 myofiber hypotrophy in congenital fiber type disproportion. *Hum Mutat*. 2009 Dec 1. [Epub ahead of print]

Lehtokari VL, Greenleaf RS, DeChene ET, Kellinsalmi M, Pelin K, Laing NG, Beggs AH, Wallgren-Pettersson C. The exon 55 deletion in the nebulin gene - one single founder mutation with world-wide occurrence. *Neuromuscul Disord*. 2009;19(3):179-81.

Ottenheijm CA, Hooijman P, Dechene ET, Stienen GJ, Beggs AH, Granzier H. Altered myofilament function depresses force generation in patients with nebulin-based nemaline myopathy (nem2). *J Struct Biol*. 2009 Nov 24. [Epub ahead of print]

Ottenheijm CA, Witt CC, Stienen GJ, Labeit S, Beggs AH, Granzier H. Thin filament length dysregulation contributes to muscle weakness in nemaline myopathy patients with nebulin deficiency. *Hum Mol Genet*. 2009;18(13):2359-69.

MTM/CNM & NM CONFERENCES IN 2009

This year marked the first MTM-CNM Family Conference held in Houston, TX in July and the 3rd Nemaline Myopathy Convention (the first ever in the US!) held in White Plains, NY in August. The conferences were wonderful opportunities for families to meet each other and learn more about different aspects of MTM, CNM, and NM. There were over 30 families in attendance at the MTM-CNM conference. The NM Convention hosted 35 individuals with NM, the largest gathering of people with NM to date! Some of the MTM-CNM lectures are now available online at <http://video.webcasts.com/events/glow001/31605/>. For pictures from this year's NM convention and updates on the next conference in 2011, visit <http://www.nemaline.org/> and click on NM Convention 2009 or 2011. Some of the NM lectures are available on DVD and can be requested by emailing mavian@verizon.net. At the NM Convention, families had the opportunity to participate in a research study led by Dr. Ching Wang of Stanford University. The study is dedicated to better defining the symptoms and interventions of NM in the hopes of developing Standard of Care Guidelines for families around the world. The information from the study is currently being analyzed in preparation for publication within the coming year.