Happy Spring!

From the Beggs Congenital Myopathy Research Program at Boston Children’s Hospital & Harvard Medical School

**Participation & More**

We are enrolling patients and their families into our studies on congenital myopathies, including centronuclear myopathy (CNM)/X-linked myotubular myopathy (XLMTM), central core disease (CCD), congenital fiber type disproportion (CFTD), multiminicore disease (MmD), myofibrillar myopathy (MFM), nemaline myopathy (NM), rigid spine muscular dystrophy (RSMD) and undefined neuromuscular diseases. 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, return the comment card, or contact our new research coordinator:

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We welcome genetic counselor Lindsay Swanson who joined the Beggs Lab in July after receiving her Master’s Degree from the University of Minnesota.

Apologies to all for this late “New Year’s” newsletter! The past year has been filled with transitions, challenges, and some great progress. We said goodbye to Elizabeth DeChene, who moved to Philadelphia to take a great new job and be closer to family, and hello to Lindsay Swanson, who has stepped into Elizabeth’s shoes with great enthusiasm and aplomb. The economy has been a particular challenge, with funding from foundations, federal grants, and philanthropic sources all contracting. Thanks so much to everybody who has contributed to support the lab. Your donations make a big difference and your support means the world to us! We have also been incredibly fortunate to benefit from fellowship grants that several senior postdocs successfully competed for, and I am pleased to report that, despite sequestration, our long standing NIH grant has recently been renewed and another new proposal is currently under review. Most importantly, none of this has stopped us from making progress! 2012 was a banner year with 16 publications describing work from the Beggs Lab. In October, we presented data at the World Muscle Society meeting in Perth, Australia on exciting new gene and protein therapies for myotubular myopathy, new zebrafish models for congenital myopathies, and also a new genetic cause for centronuclear myopathy. Just this last month, the protein therapy manuscript, and a seminal paper describing our new mouse model for multi-minicore myopathy due to selenoprotein N mutation were published. Together with your support and collaboration, we look forward to continuing our work to make a difference for all our families with congenital myopathies.

UPCOMING EVENTS

The **MTM-CNM Family Conference** is July 26-28 in Minneapolis, MN, USA (www.mtm-cnm.com)

For more info, email warderin@comcast.net

Our research with zebrafish continues to help our understanding of the congenital myopathies. Zebrafish make a wonderful model for muscle disease because they breed and develop quickly, and their muscle structure is remarkably similar to humans. Dr. Vandana Gupta’s research on identifying genes that result in congenital muscle disease recently identified zebrafish with a mutation in the laminin-α2 (merosin) gene. Laminin-α2 is a protein that provides stability to muscle structure. The fish without laminin-α2 show severe skeletal muscle dystrophy with eye and brain abnormalities, just like humans who have been diagnosed with merosin-deficient congenital muscular dystrophy (MDC1A). Vandana is collaborating with members of the Kunkel Lab to screen for drugs that allow these fish to develop normally and is now developing drug screens with ryanodine receptor (RYR1) mutated fish, which model human minicore myopathy.

Vandana has also focused her research on α-actinins. These are actin-binding proteins that make up a family of very similar proteins. The α-actinins show identical activities in most in vitro ("test tube") experiments and appear to be able to substitute for each other in laboratory experiments. Vandana’s zebrafish studies showed that α-actinins work in different parts of the bodies of zebrafish and express at different times during zebrafish development. Loss of α-actinin-2 caused skeletal muscle and heart abnormalities in developing fish that could not be rescued by highly similar α-actinin-3. These studies showed that even though α-actinins have similar genetic sequence, the different forms have evolved differently to optimize their function.

There is much more activity in the lab on this front. In two new projects just getting started, Dr. Ozge Ceyhan is generating transgenic actin zebrafish for their use in developing therapies for nemaline myopathy. Graduate student Laura Smith has been actively involved in developing zebrafish models for centronuclear and minicore myopathies caused by defects in the BIN1, DNM2, and SEPN1 genes.

The Beggs Lab is actively using whole genome sequencing (WGS) in their approaches to learning more about the genetics of the congenital myopathies. In the past year, three new genes discovered by WGS were published by the Beggs Lab. The new genes are:
1. MEGF10 causing multiminicore disease (Boyden et al.)
2. CCDC78 causing centronuclear myopathy with minicores (Majczenko et al.)
3. GTDC2 causing a form of muscular dystrophy (Manzini et al.)

At the World Muscle Society Conference in Perth, Australia in October, Dr. Ozge Ceyhan announced the discovery of mutations in the titin gene (TTN) in patients with centronuclear myopathy including in AJ Foye who was part of the CLARITY Challenge. This was the first time a link between TTN and CNM has been found. For the Foye family, they finally have an answer for why their son AJ has centronuclear myopathy. This is an exciting breakthrough for centronuclear myopathy research and for families like the Foyes who have been looking for answers over a decade.

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RESOURCES FOR PATIENTS

General Resources:
- Muscular Dystrophy Association (www.mdausa.org)
- GeneReviews (www.genereviews.org)
- Genetics Home Reference (http://ghr.nlm.nih.gov/)

Connections to Families:
- Congenital Muscle Disease International Registry (www.cmdir.org)
- Facebook and Yahoo Groups
- My MDA at mymda.mda.org
  Search under: CFTD, Minicore, Myopathy, Myotubular, or Nemaline

Condition Specific Resources:
- CFTD
  The Caytlon Wheeler Foundation
  (www.caytlonwheeler.org)
- CNM/MTM
  The Joshua Frase Foundation (www.joshuafrase.org)
  The Information Point for CNM/MTM
  (www.centronuclear.org.uk)
  MTM Resource Group (www.mtmrg.org)
  Myotubular Trust (www.myotubulartrust.com)
- NM
  The NM Support Group (www.nemaline.org)

A MOUSE MODEL FOR COFILIN-2 RESEARCH

In 2007, researchers from the Beggs Laboratory identified cofilin-2 (CFL2) to be the sixth gene mutated in nemaline myopathy with minicores. This year, Dr. Pankaj Agrawal and his team developed a mouse model with changes or alterations in the CFL2 gene. Mutations of CFL2 result in reduced amounts or altered forms of cofilin-2, a protein important for maintaining the function of muscle. A mouse model was created because this animal can help us to understand the mechanism for how changes in CFL2 cause congenital myopathy. We were able to decrease CFL2 gene expression in mice and show that these mice had symptoms similar to those observed in patients with severe muscle weakness. These research findings were published in the journal Human Molecular Genetics (Agrawal et al.). These studies have established the role of cofilin-2 in maintaining muscle function. We hope to continue studying these “knockout” or decreased CFL2 mice for clues as to the function of cofilin-2 in maintaining healthy muscle. Additionally, this year we collaborated with a research group in the Netherlands to describe the second known family with a mutation of CFL2 (Ockleoen et al.).

CLINICAL GENETIC TESTING

Commercial genetic testing is now available for many of the genes associated with the congenital myopathies. More information is available at www.ncbi.nlm.nih.gov/gtr/

DISEASE ASSOCIATED GENES (% of cases with mutations in given gene)

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ASSOCIATED GENES</th>
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<tbody>
<tr>
<td>CCD</td>
<td>RYR1 (&gt;90%)</td>
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<tr>
<td>CFTD</td>
<td>TPM3 (20-30%)</td>
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<tr>
<td></td>
<td>RYR1 (?)</td>
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<tr>
<td></td>
<td>ACTA1 (6%)</td>
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<tr>
<td></td>
<td>SEPN1/MYH7</td>
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<tr>
<td></td>
<td>TPM2 (rare)</td>
</tr>
<tr>
<td>CNM</td>
<td>DNM2 (?)</td>
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<tr>
<td></td>
<td>RYR1 (?)</td>
</tr>
<tr>
<td></td>
<td>BIN1 (rare)</td>
</tr>
<tr>
<td></td>
<td>TTN (?)</td>
</tr>
<tr>
<td>XLMTM</td>
<td>MTM1 (&gt;80%)</td>
</tr>
<tr>
<td>MmD/RSM</td>
<td>SEPN1 (30-50%)</td>
</tr>
<tr>
<td></td>
<td>RYR1 (?)</td>
</tr>
<tr>
<td></td>
<td>ACTA1 (rare)</td>
</tr>
<tr>
<td>NM</td>
<td>ACTA1 (15-25%)</td>
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<tr>
<td></td>
<td>TPM2/TMP3 (&lt;10%)</td>
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<tr>
<td></td>
<td>NEB (~50%)*</td>
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<td></td>
<td>TNNT1/CFL2 (rare)</td>
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*Full sequencing and specific testing for the exon 55 deletion, a mutation more common in the Ashkenazi Jewish population, are both available

WE WOULD LOVE TO HEAR FROM YOU!
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Dr. Jeffrey Widrick joins the Beggs Lab from Spaulding Rehabilitation Hospital, Boston. Dr. Widrick’s background is in muscle physiology. His research uses isolated muscle and single muscle cells to understand how mechanisms underlying contraction are altered in neuromuscular disease.
RECENT KEY PUBLICATIONS


RECENT EVENTS

Congratulations to Elizabeth DeChene, MS, CGC, who has started a new position at Children’s Hospital of Philadelphia, and to Christine Mahoney, our previous research assistant, who is pursuing her master’s degree in Organizational Psychology at Columbia University. Congratulations also to Marissa Viola, who is pursuing her PhD at the University of Rhode Island. A warm welcome to Dr. Ozge Ceyhan, a new post-doctoral research fellow, to Dr. Huan Ling Wang who is a visiting associate professor from Huazhong Agricultural University in China, to Dr. Shideh Kazerounian, a senior research fellow, and to Nicholas Marinakis, a new research assistant in the lab.