Happy Holidays!

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

Happy New Year!

During 2011, the Beggs Congenital Myopathy Research Program expanded our insight into causes and potential therapies for the congenital myopathies (CMs) and related neuromuscular diseases. Through the use of zebrafish models and whole genome and exome sequencing, Drs. Vandana Gupta and Pankaj Agrawal endeavored to identify new genes that may be associated with the congenital myopathies and other neuromuscular conditions. Drs. Michael Lawlor and Behzad Moghadaszadeh utilized mouse models of disease in order to better understand the functions of MTM1, SEPN1 and ACTN2/3 in normal and diseased muscle. During the coming year, we will strive to further broaden our understanding of the CMs, in hopes of improving diagnosis and treatment of individuals and families in the future.

Thank you for your participation and support!

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, to request to be removed from the mailing list, or to inquire about making a donation, please visit our website www.childrenshospital.org/research/beggs or return the comment card (pg. 3) or contact our research coordinator:

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PLANNING A VISIT TO BOSTON THIS YEAR?
We would love to meet you and give you a tour of the lab!

DO YOU HAVE A SEPN1 MYOPATHY?
We are actively recruiting patients with known or possible alterations in the SEPN1 gene in preparation for potential clinical trials within the next few years.
A MOUSE WITH A Milder FORM OF XLMTM

Dr. Christopher Pierson, a former member of the Beggs Laboratory, recently established a new mouse model of a less severe form of X-linked myotubular myopathy (XLMTM), an X-linked type of centronuclear myopathy caused by changes or alterations in the MTM1 gene. Mutations of MTM1 result in reduced amounts or altered forms of myotubulin, a protein important for communication within the muscle. The Beggs team has previously worked extensively with the severe “knock out” MTM1 mouse that makes no myotubulin at all. These mice only live for 8 weeks, making it difficult to utilize them for long-term testing of potential therapies. In addition, these severe XLMTM mice are not a perfect model for XLMTM in humans, since some boys have milder symptoms. The new, less severe mouse model has a change in the MTM1 gene that allows the body to make small amounts of altered myotubulin, resulting in milder symptoms. The difference in severity between the two mouse models helps to explain some of the variation in the severity of symptoms seen among boys with XLMTM. This milder mouse model will serve as a valuable tool for understanding XLMTM and broadening the options for testing of therapies for XLMTM and other congenital myopathies. We are currently utilizing these mice to test a variety of treatments, including myostatin inhibition, which we described in our 2010-2011 newsletter, as well as other approaches such as treating abnormal communication between the nerve and the muscle in patients with XLMTM.

THE CLARITY CHALLENGE: BRINGING WHOLE GENOME SEQUENCING TO THE CLINIC

In early 2012, Children’s Hospital Boston will launch the CLARITY (Children’s Leadership Award for the Reliable Interpretation and appropriate Transmission of Your genomic information) Challenge, a project led by Isaac Kohane, MD, PhD; Alan Beggs, PhD; and David Margulies, MD. The goal of the Challenge is to improve the way we analyze the results of a new genetic testing technology called whole genome sequencing (WGS) and to report those results back to doctors and patients. Our genome contains all of our genetic material, including all of our genes. Recent scientific advances now allow us to analyze a person’s whole genome to look for gene changes or alterations that may be involved in disease. However, WGS produces a lot of information that we do not yet understand how to interpret, including information about gene alterations that have never been reported, many of which are benign. Genetic testing companies are hoping to offer WGS for use in doctors’ offices within the next few years, yet there are still no widely accepted standards for how the genome should be analyzed or what information should be reported to patients.

The CLARITY Challenge will invite researchers from around the world to analyze the whole genome sequences of three families - one family with nemaline myopathy, a second with centronuclear myopathy, and a third with cardiac disease – who are suspected to have a genetic basis for their conditions. Researchers who participate in the Challenge will be asked to develop the best methods for identifying and reporting back the genetic alterations that are associated with disease in each family. We hope the CLARITY Challenge will help develop clear and concise standards for WGS, thus improving the identification of disease-causing gene changes and the medical care of families in the future.

A NEW ZEBRAFISH MODEL OF CONGENITAL MUSCULAR DYSTROPHY

Zebrafish make an excellent model for muscle disease because they breed and develop quickly and their muscle structure is remarkably similar to humans. The Beggs Lab utilizes zebrafish to identify new genes that may be associated with congenital myopathies. In the lab, Dr. Vandana Gupta and her team developed a zebrafish with an alteration in the dag1 gene, resulting in no production of dystroglycan. Dystroglycans are important proteins in muscle that help stabilize the outer wall of the cell (cell membrane) through interactions with other proteins that form a special complex called the dystrophin-glycoprotein complex (DGC). Alterations in the DAG1 gene are only rarely identified in humans, but changes are seen in many genes involved in the DGC. The dag1 fish has brain malformations, eye defects and muscle abnormalities that are consistent with symptoms in people who have alterations in genes in the DGC. Therefore, the dag1 mutant offers a useful model for future studies on muscular dystrophies, such as Walker-Warburg syndrome and Muscle Eye Brain disease.

Due to their rapid development and small size, zebrafish are a powerful tool for testing new therapies for neuromuscular disease. Through the use of a specialized machine, we can track zebrafish movements while they swim and record how their movements change after they are treated with different medications. Drugs that increase the amount of movement may be potential therapies for neuromuscular disorders. We are currently using the dag1 fish to search for drugs that may improve muscle function. Further testing will determine if these drugs show promise in additional zebrafish and other disease models, such as mice or dogs. In addition to the dag1 fish, the Beggs lab is also establishing zebrafish models of multiminicore disease (SEPN1) and other RYR1-related myopathies, such as centronuclear myopathy and central core disease.
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:
  - Facebook Groups at www.Facebook.com
  - YouTube Groups at groups.google.com
  - HealthShare Groups at http://healthsharegroups.org
  - My MDA at mymda.mda.org
  - Search under: CFTD, Minicore, Myopathy, Myotubular, or Nemaline

Condition Specific Resources:
CFTD:
  - The Cayton Wheeler Foundation (www.caytonwheeler.org)

CNS/MST:
  - The Frase Foundation (www.joshuafrase.org)
  - The Info Point for CNS/MST (www.centroneural.org.uk)
  - MTM Resource Group (www.mtmrg.org)

NM:
  - The NM Support Group (www.nomalne.org)
  - A Foundation Building Strength for NM (www.buildingstrength.org)

GENE THERAPY FOR XLMTM IS PROMISING IN DOGS

Gene therapy is a powerful approach for treating many genetic diseases, including the congenital myopathies (CMs). Genes are instructions that tell our body how to grow and develop. Each gene encodes a protein that performs a specific job in our body. The CMs are caused by having an abnormal version of a “muscle” gene that does not work properly, due to the presence of a change or mutation in the gene. Gene therapy allows scientists to replace a gene that is not working properly. It is unlikely to work for all types of gene alterations, but it shows a lot of promise for people with gene changes that cause a decrease in the amount of protein that a gene produces. Gene therapy allows scientists to insert a working gene into a harmless virus such as “adeno-associated virus” (AAV) and then inject or infuse the person with the AAV containing the working gene. Like the common cold, the virus can spread through the body, inserting the working gene into the person’s cells and improving or curing their myopathy. In collaboration with the Beggs Lab and the Joshua Frase Foundation, Dr. Casey Childers and his team at Wake Forest University established a colony of dogs with the canine version of X-linked myotubular myopathy (XLMTM). Working with the French group Généthon who produced the virus and with support from the American and French Muscular Dystrophy Associations, Dr. Childers and his team recently conducted the first tests of gene therapy in the XLMTM dogs with an AAV containing MTM1 (the gene associated with XLMTM). The initial results are promising, suggesting that gene therapy may be an effective treatment for XLMTM and other CMs. Our teams are now planning additional studies in order to determine its effectiveness and identify side effects. If gene therapy proves to be successful in the dogs, then it will open up the possibility of a clinical trial for boys with XLMTM and testing this approach in other CMs.

COMMENT CARD

NAME OF PERSON COMPLETING CARD:_________________________________________

QUESTION/COMMENT:________________________________________________________

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WE WOULD LOVE TO HEAR FROM YOU!
For more information about our research and the topics in this newsletter or for suggestions on future topics, please return this card to:

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RECENT KEY PUBLICATIONS & EVENTS

Congratulations to Michael Lawlor, MD PhD, who established a new neuropathology laboratory at Children’s Hospital of Wisconsin, where he will continue to study XLMTM and other neuromuscular diseases. A Warm Welcome to: Pedro Ciarlini, MD, a neuropathologist in the Harvard Longwood Ave. Neuropathology Program who is joining the lab this winter, and to our new research assistant, Christine Mahoney, BA, who took over her position from Jennifer in June, 2011.


