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Dystonia Research Program at MGH

In the first edition of our Dystonia Update, we introduced you to the cycle of genetic research, which starts with people, then goes to DNA to cells to animals and ends with people. In this newsletter, the second edition of the Dystonia Update, we want to show you how projects in our Dystonia Program help to move the genetic research cycle forward.

We approach dystonia research from many angles or, in this case, many points within the genetic research cycle (see page 5 for figure). We feel that this approach provides us a broad perspective on dystonia, which makes it easier for us to find answers to our research questions. In addition, techniques, ideas and insights in one area can fuel inspiration in the next. It is our hope that cultivation of long-term professional relationships, new collaborations, and world-renown expertise will drive dystonia research forward and that our research answers will be translated into advances in the care and treatment of people with dystonia.

There are six projects in our Dystonia Program (DP) at Massachusetts General Hospital included in our many-angled approach. Each of the six areas has research staff dedicated to its projects and some research staff members work on multiple DP projects. This ensures that (1) individual projects have the manpower and resources to move forward, and (2) we maintain a perspective on the DP as a whole.

DP Project 1
In addition to coordinating all six Dystonia Program projects, Dr. Breakefield runs the cell biology – TorsinA component of the DP. The activities of the cell biology – TorsinA project were highlighted in the 1st edition of the Dystonia Update – “The TorsinA Protein: The foundation of step four” on page 2.

DP Project 2
Dr. Laurie Ozelius, who is an associate professor at Mount Sinai School of Medicine, coordinates the genetics portion of the DP. Genetic experiments take place both at Mount Sinai and MGH. A few of the activities within the genetics group were discussed in the “Dystonia-Related Gene Update: Working on step three” article in the first Dystonia Update.

DP Project 3
Through the DP, we are exploring the biology of dystonia in two animal models: the mouse and drosophila (fruit flies). Dr. Standaert and Dr. Sharma oversee the dystonia research related to transgenic mice at the University of Alabama and Massachusetts General Hospital, respectively. A description of the transgenic mice developed at MGH appeared in the 1st edition of the Dystonia Update on page 3.

(continued on p. 5)
DYT1 Dystonia and the Developing Brain

By Pradeep Bhide, Ph.D.

We are still learning about how changes in the DYT1 gene produce the symptoms of DYT1-associated dystonia (early onset torsion dystonia). It is clear that the symptoms, such as twisting in the legs or arms, generally begin at a young age when the brain is still maturing. In particular, the part of the brain that controls muscles (the motor system) continues to develop during childhood. This leads us to believe that the DYT1 gene (and the protein that the DYT1 gene makes, torsinA) has something to do with the development of the brain’s motor systems. If there is a mutation or change in the DYT1 gene, and thus the torsinA protein, development of the brain’s motor system may be compromised.

If mutations in the DYT1 gene compromise the brain’s motor system early in development, we can guess that the onset of symptoms represents a point in time when microscopic changes in the motor system caused by the changed torsinA protein reach or cross a threshold. Indeed, we could speculate that DYT1 mutations begin to exert small but significant effects on the developing motor system early in life and that the changes accumulate and manifest as symptoms of dystonia either upon reaching a threshold or upon encountering some other environmental inductive signal.

We felt that a clear understanding of the role of torsinA in the developing brain may give us clues about how changes in the DYT1 gene may impair development of the motor system and predispose people to dystonia. To improve our understanding, we first studied when the torsinA protein is active in the developing brain of a normal mouse (a mouse with normal torsinA genes). We found that torsinA is present in brain cells early in fetal development. Next, we examined if torsinA plays a role in either of the two major events that occur in the fetal brain. (See sidebar on fetal brain events) To do this, we studied mice that were genetically altered so that they do not have any torsinA protein, which are also known as torsinA “knock-out” mice (provided by Dr. Yuqing Li at the University of Alabama). In the mice that do not have any torsinA protein, we are studying the production (neurogenesis) and movement (neuronal migration) of a specific type of brain cells important in motor function, which are called GABA cells. It is possible, although entirely speculative at this stage, that a change in the DYT1 gene impairs the normal development of the motor systems in the brain, and these changes may serve as the reasons for the motor impairments in people with DYT1-associated dystonia.

Acknowledgments for their contribution to this work go to Deirdre McCarthy, Juan Zeng and John Sims.

Volunteers Needed for DYT1 Dystonia Research Study

Researchers at Massachusetts General Hospital are conducting a research study to understand how changes in the DYT1 gene may affect the ability to learn specific movements.

Any adult member of a family in which one individual has a mutation or change in the DYT1 gene can take part in this research study. Those who carry a change in the DYT1 gene (whether or not they have symptoms) as well as family members (who may or may not carry mutation in the DYT1 gene) are all eligible to take part.

Adults can NOT take part if:
- Under 18 years old
- Had brain surgery (incl. DBS)
- Have dystonia symptoms that prevent completion of research tests

Adults who take part in this research agree to a physical exam, videotaping, a blood draw, and a series of “motor learning” tests (similar to video games). The motor learning tests are non-invasive and will cause no discomfort. Research participants also provide medical and family history information.

Taking part requires traveling to Boston for appointments at Massachusetts General Hospital (MGH) and Massachusetts Institute of Technology (MIT). Participation requires at least one overnight stay in a hotel. The entire study can be completed in two and a half consecutive days. We help participants arrange transportation and hotel stays, if the participant comes from outside the Boston area. All participants who complete the study will receive $75. There are no direct benefits to the people who take part, and research participants do not learn the results of their testing.

If you are interested in learning more about taking part in this research, please contact us. The Principal Investigator, Nutan Sharma, M.D., Ph.D., may be reached at (617) 724-9234 or nsharma@partners.org. The Study Coordinator, Trisha Multthaupt-Buell, M.S., can be reached at (617) 726-5470 or tmulthaupt@partners.org.

Because DYT1 dystonia is uncommon and success of this study depends on the participation of members of DYT1 families, even if you do not have DYT1 dystonia, we ask your help in informing individuals with DYT1 dystonia of the opportunity to take part in this study.

Thank you for considering this opportunity to help us learn more about dystonia.
Beginning a Search for New Drugs to Treat Dystonia

By Cristopher Bragg, Ph.D.

The Department of Neurology at Massachusetts General Hospital is the hub of an exciting new research collaboration focused on identifying new therapeutic compounds for early onset dystonia. Earlier this year, the Bachmann-Strauss Dystonia and Parkinson’s Foundation (BSDPF) awarded funds to Dr. Xandra Breakefield and Dr. Cristopher Bragg, both at MGH, and to Drs. Guy and Kim Caldwell at the University of Alabama. The investigators have formed a unique three-way partnership to maximize their efforts to find new drug candidates to treat dystonia.

Dr. Bragg, who is also affiliated with the Broad Institute in Cambridge, met the Caldwells at a DMRF dystonia research workshop in 2006. They realized that their laboratories were both working to find new treatment options for dystonia. Dr. Bragg’s group uses a screening technology developed at the Broad Institute to identify compounds which bind directly to torsinA. TorsinA is the protein associated with early onset dystonia. The Caldwells took a different approach, using genetically modified roundworms to test compounds which affect the function of torsinA. The two groups agreed to share their discoveries and eventually recruited Dr. Breakefield to join their collaboration as well.

Dr. Breakefield’s lab identified the DYT1 gene encoding torsinA and the mutation underlying most cases of early onset dystonia in 1997. Her team has since developed a novel method to look at one function of torsinA in human cells obtained from people with DYT1-associated dystonia and unaffected control subjects. Under the terms of this new collaboration, Dr. Bragg and the Caldwells have agreed to exchange new drug candidates identified by their screening efforts for testing in the other model system. They will also provide these compounds to Dr. Breakefield, who will determine if any new drug candidates improve torsinA-related function in cells from people with DYT1-associated dystonia.

The investigators hope that by examining a wide range of compounds in multiple contexts, including cells from people with DYT1-associated dystonia or cells with mutant torsinA in particular, it may be possible to identify potential new drug candidates for dystonia. By providing funds for this partnership, the Bachmann-Strauss Dystonia and Parkinson’s Foundation has indeed shown its strong commitment to initiatives aimed at treating dystonia.

Clinical Corner

Great news! The Partners Dystonia Center is expanding! Lisa Paul, a nurse practitioner, has recently started in the Dystonia Center on a full time basis. Lisa works closely with Dr. Sharma to provide care to children and adults with dystonia. What will this mean? It will mean more available appointments for close follow up of new medication/treatment starts and decreased wait times for new patient appointments.

Some of our goals over the next year will include the development of educational materials for the patient and the family. We have ideas but we’d love to know the kinds of things that you would like to learn about.

Please send your ideas and questions to: DystoniaResearch@partners.org

For instance: Did you know?

Dystonia may affect a single body part or may affect more than one body part, but the reasons for this remain unclear. We are working to unravel the mysteries to have a better understanding of how we can treat dystonia.

Typically, the treatment of choice for most focal dystonias is botulinum toxin injections, although oral medications occasionally may be helpful.

In some cases, surgical treatment of dystonia may be an option but is usually reserved for patients in whom other forms of therapy fail.

Dystonia symptoms are made worse by stress (physical or emotional), illness (such as a cold or flu) or fatigue due to lack of sleep or over-doing it. These things can make it feel as if your medications are not working. To help avoid this problem, limit your activities (or their length), rest often, drink plenty of fluids if you are sick with a cold or flu and get plenty of sleep. For some people, it may take 1-2 weeks to feel like your symptoms are back to normal or under control.

HAVE PATIENCE!
Dr. Xandra Breakefield’s recent publications:

   Dopamine release is impaired in a mouse model of DYT1 dystonia.
   Summary: Please see summary under Dr. Sharma’s publications.

   Mutant torsinA interferes with protein processing through the secretory pathway in DYT1 dystonia cells.
   Proceedings of the National Academy of Sciences of the United States of America (PNAS) 2007; 104: 7271-7276.

3. Breakefield, X. and Standaert D.
   Neurotransmitter Disorders: Torsion Dystonia

   TorsinB expression in the developing human brain.
   Brain Research. 2006; 1116:112-119.

   Effects of genetic variations in the dystonia protein torsinA: Identification of polymorphism at residue 216 as protein modifier.
   Human Molecular Genetics, 2006; 15:1355-1364.
   Summary: In addition to the GAG deletion in the DYT1 gene that is associated with early-onset generalized dystonia, three other sequence variations have been found in the coding region of the DYT1 gene. One of these other variations is a single nucleotide polymorphism (SNP) where aspartic acid (D) is replaced by histidine (H) at residue 216 in the amino acid chain of the torsinA protein. Both D216H and the GAG deletion cause changes in the torsinA protein near an area where other proteins interact with torsinA. Cells with D216H alone or the GAG deletion alone look similar to each other but different from normal cells. However, if a cell has both the D216H and the GAG deletion, it looks more like normal cells than when either change is by itself. This might mean that D216H can provide more information about who develops symptoms of dystonia and who does not.

   Genetic evaluation in primary dystonia.

7. Vasudevan, A., Breakefield, X.O., Bhide, P.
   Developmental patterns of torsinA and torsinB expression.
   Brain Research. 2006; 1073-1074:139-145.
   Summary: See page 2.

   RNAi blocks DYT1 mutant torsinA inclusions in neurons.
   Neuroscience Letters. 2006; 395:201-205.
   Summary: Cells with the DYT1 GAG deletion look different compared to cells with a normal DYT1 gene. We made short pieces of inhibitory RNA (RNAi) that can bind to the DYT1 message with the GAG deletion. Cells mixed with both the DYT1 GAG deletion and the RNAi that can bind to the GAG deletion looked like cells with the normal DYT1 gene. This RNAi selectively blocked expression of the DYT1 GAG deletion so that the cells appeared normal. These short pieces of RNA may have the potential to reduce the affects of the DYT1 GAG deletion.

   Dystonia-causing mutant torsinA inhibits cell adhesion and neurite extension through interference with cytoskeletal dynamics.

Dr. Nutan Sharma’s recent publications:

   White matter abnormalities in dystonia normalize after botulinum toxin treatment.
   NeuroReport; 2006; 17(12):1251-1255.
   Summary: Research subjects with cervical dystonia and hand dystonia and research subjects without dystonia had an MRI with diffusion tensor imaging. The brain images of people with dystonia were different from people without dystonia. However, 4 weeks after botulinum toxin injections, the brain images of people with dystonia “normalized” and were the same as people without dystonia. These findings show that peripheral muscle activity can have effects on the central nervous system and may lead to new insights about what causes dystonia.

   Altered responses to dopaminergic D2 receptor activation and N-type calcium currents in striatal cholinergic interneurons in a mouse model of DYT1 dystonia.

   Dopamine release is impaired in a mouse model of DYT1 dystonia.
   Summary: There is no difference in the amount of dopamine or dopamine receptors in the brain tissue of transgenic mice compared to the brain tissue to non-transgenic mice. However, transgenic mice that express the human DYT1 GAG deletion show decreased amphetamine-induced dopamine release in the brain compared to non-transgenic mice. This suggests that the DYT1 GAG deletion causes a problem in the release of dopamine. The abnormal release of dopamine could lead to the motor learning problems seen in these transgenic mice and may contribute to the clinical symptoms of the human disorder.

4. Sharma, N.
   Gene Repression or Imprinting: Rett Syndrome.

5. Sharma, N.
   Patient Preference in Botulinum Toxin for Writers Cramp.
   Journal: Journal Watch Neurology. 2007; Oct 2

To find these articles or read other cutting-edge dystonia research:

- Ask your local librarian
- Use the internet
  - PubMed - Search for specific articles or topics
    [www.pubmed.gov](http://www.pubmed.gov)
- Ask your doctor
- Contact the MGH Dystonia Research Program
  [DystoniaResearch@partners.org](mailto:DystoniaResearch@partners.org)
Dr. Gusella, who is also the director of the new Center for Human Genetic Research at MGH, coordinates the dystonia drosophila project. Look for more about the drosophila in an upcoming edition of this newsletter!

DP Project 4:
In our effort to understand what causes dystonia, we want to investigate the role of torsinA and dystonia-related genes and proteins in early development. You can find an article written by Dr. Bhide, who oversees the developmental dystonia projects, on page 2.

DP Project 5:
When we find new genes and proteins related to dystonia, they can be a logistical challenge to study because the tools and reagents necessary to see and follow the genes and proteins have not been developed. To help identify and solve some of these logistical problems quickly and effectively, Dr. Ramesh runs the dystonia antibody core that designs and manufactures chemicals that allow us (and other researchers) to identify torsinA and torsin-related proteins when doing experiments. Dr. Ramesh’s projects led to the development of torsinA antibodies (markers) that are now available to dystonia researchers world-wide.

DP Project 6:
The final DP project is the dystonia clinical core, which is coordinated by Dr. Nutan Sharma. The clinical core is the beginning and end of the genetic research cycle and all of the projects in the Dystonia Program. The clinical core researchers meet the families and individuals with dystonia who want to take part in research studies. These families and individuals share their experiences, medical histories, blood samples, brain images and other information. This information and the samples are used to inform and drive the other projects in the Dystonia Program. And when the Dystonia Program researchers find information useful to the families and individuals with dystonia, the clinical core research staff ensure that those who were generously gave their time and information to dystonia research, get this valuable information back.

In these ways, each of these six projects fits within the genetic research cycle and helps to keep the wheel turning.

In Appreciation

In addition to each of you who supports our research with your time, experience and insight, we would like to convey a special thank you to the financial sponsors of our dystonia research at Massachusetts General Hospital.

The National Institutes of Health: The National Institute of Neurological Disorders and Stroke
Grant Title: Molecular Etiology of Early Onset Torsin Dystonia (Breakefield)
Grant Title: The Role of DYT1 Mutation in Dystonia (Sharma)

The Dystonia Medical Research Foundation
Grant Title: Motor Learning in DYT1 Dystonia (Friedman)

The Bachmann-Strauss Dystonia and Parkinson Foundation
Grant Title: Genetic Intervention Strategies for DYT1 Dystonia (Breakefield)

The Jack Fasciana Fund for the Support of Dystonia Research

Lockwood Family Fund
Grant Title: Targeted Search for Dystonia Genes (Sharma)

The National Parkinson's Foundation
Grant Title: TorsinA: Critical for Dopamine Neuron Survival (Sharma)
Learn more about:

- The search for new treatments
- Dystonia and early development
- The many parts of the Dystonia Research Program