



Thought Leaders Gather to Share Dystonia Research Progress & Strategize Future Directions



Dr. Mahlon R. DeLong (L) is transitioning to Scientific Director Emeritus and Dr. Joel S. Perlmutter is DMRF's new Scientific Director.

The annual meeting of the Medical & Scientific Advisory Council (MSAC) is a gathering of experts to guide the DMRF's scientific and research efforts. This year's meeting, on February 7–8, in San Antonio, Texas, was notable not only for the caliber of presentations and investigators who attended but also a change in MSAC leadership. Mahlon R. DeLong, MD has retired after 25 years of exceptional service to DMRF as Scientific Director. Dr. DeLong will remain involved with the DMRF as Scientific Director Emeritus and Lifetime Honorary Board Member. Joel S. Perlmutter, MD of Washington University in St. Louis, and Co-Director of the Dystonia Coalition, now serves as DMRF Scientific Director. As Scientific Director, Dr. Perlmutter will work closely with DMRF Chief Scientific Advisor Jan Teller, MA, PhD and DMRF Vice President of Science Richard Lewis, MD in planning and evaluating the Foundation's scientific efforts. He will also serve as the Chairperson of the DMRF MSAC and offer guidance to the Board of Directors on dystonia research. Look for more information about these dystonia leaders and their vital contributions to dystonia research in a future *Dystonia Dialogue* newsletter.

“Dystonia is a disease that can solve many puzzles of the brain. It is a network disorder with implications for understanding motor control.”

~ Jan Teller, MA, PhD, Chief Scientific Advisor

The MSAC meeting featured a number of dynamic presentations, representing the very latest scientific advancements, and delivered by highly influential and accomplished investigators:

Joan Miller Keynote Lecture:

Solving the Dystonia Puzzle: The Quest for a Cure (7 Years Later)

Pedro Gonzalez-Alegre, MD, PhD

A Search for Final Common Pathways in Genetic Dystonias

Michelle Ehrlich, MD

Using Human Genetics to Explore the Functional Neuroanatomy of Dystonia Syndromes

Niccolo Mencacci, MD, PhD

Deep Brain Stimulation for Dystonia: The UCSF Experience

Jill Ostrem, MD

Using Brain Activity to Guide Dystonia Therapies

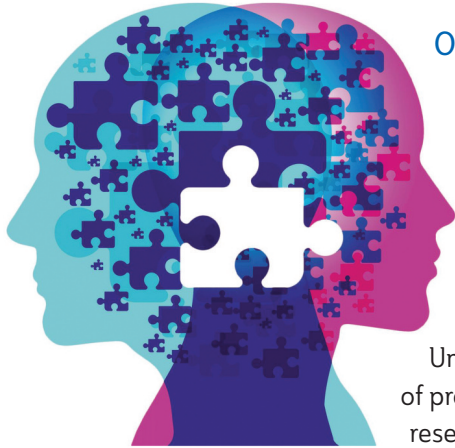
Roy Sillitoe, PhD

Dystonia: Let's Move Forward

Joel S. Perlmutter, MD

Codrin Lungu, MD, Federal Liaison from the National Institute of Neurological Disorders & Stroke (NINDS), reported on outcomes from a recent NINDS workshop dedicated to dystonia in which DMRF participated.

Investigators Pursue Mystery of TorsinA



One of the dystonia field's greatest puzzles is how and why changes in a mysterious protein in the brain lead to a disabling inherited type of dystonia. Mutated TorsinA is notorious for its role in causing most cases of isolated childhood dystonia, but it is also suspected to play a role in additional types of dystonia.

Understanding the role of proteins in dystonia is a research priority because it may lead to new treatment strategies. TorsinA is an important potential drug target. A great deal of effort is being put into exploring strategies to stop or reverse the negative consequences of abnormal TorsinA.

TorsinA Highlights: What are we learning?

Dystonia investigators around the world are working to understand how TorsinA functions normally and what cellular functions go wrong when the protein is abnormal due to genetic changes in the DYT1 gene. Here are just a few highlights of what investigators have learned.

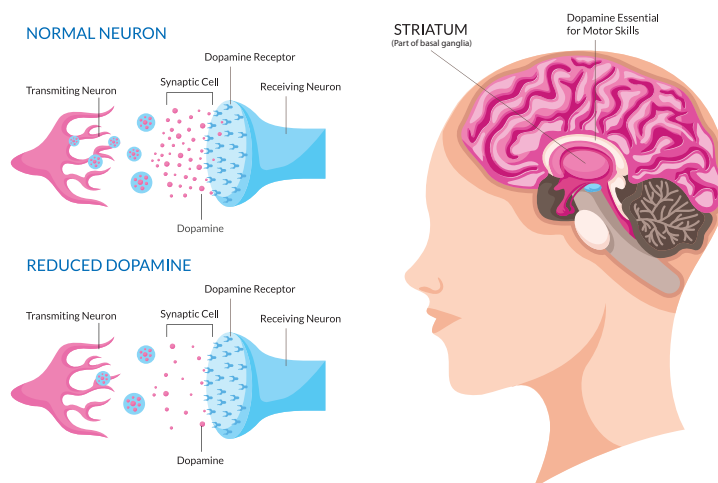
- **TorsinA comes from a big family.** TorsinA belongs to the AAA+ ATPase family of proteins, which has many roles in cells. They break down a molecule called ATP and use the energy released to sort and transport other proteins through specific pathways in the cell.
- **TorsinA has a complicated social life.** TorsinA is found primarily in brain cells (neurons) and interacts with numerous proteins. Uncovering the proteins with which TorsinA interacts is key to understanding its function. DMRF grant recipient C. Patrick Lusk, PhD of Yale University used a sophisticated yeast model to systematically study proteins with connections to TorsinA. Dr. Lusk's team showed that TorsinA interacts with a previously unassociated protein, SUN 1. They also demonstrated differences in the behavior of normal and mutant TorsinA, which suggest new directions to better understand the negative effects of abnormal TorsinA in cells.
- **TorsinA lacks self-motivation.** Two proteins called LULL1 and LAPI activate TorsinA. This makes TorsinA curiously different from other members of the AAA+ ATPase family, which are self-starters.
- **TorsinA slacks off without friends around.** When TorsinA becomes abnormal due to genetic changes, it cannot bind with LULL1 or LAPI and therefore cannot activate to do its job in the cell. LULL1 and LAPI may provide opportunities to manipulate TorsinA for therapeutic purposes.
- **TorsinA wanders off when not well.** Inside every human cell, a floppy barrier called the nuclear envelope separates genetic material from the rest of the cell. TorsinA commonly hangs out in the nuclear envelope. However, when TorsinA becomes dysfunctional, it accumulates in the endoplasmic reticulum, which bumps up against the nuclear envelope. Abnormal TorsinA causes deformities in the nuclear envelope. Correcting these deformities could be an important therapeutic strategy.
- **TorsinA has no business in certain cell processes.** An important study led by DMRF grant recipient N. Charles Harata, MD, PhD investigated the effects of dysfunctional TorsinA on the Golgi apparatus, a machinery in the cell that sorts and processes proteins. Through sophisticated techniques, Dr. Harata and his team concluded that dysfunctional TorsinA exerts no damage to the Golgi apparatus, which can help future investigations focus in other directions to understand the role of TorsinA in cells.

New Insights into Inconsistent Patient Response to Oral Meds

AT A GLANCE

- A protein called **RGS9-2** regulates dopamine signaling in the basal ganglia.
- **RGS9-2** may be an important new therapeutic target for dystonia.

Individuals with dystonia vary in their response to oral medications. Levodopa, an oral medication that boosts dopamine, can dramatically reduce dystonia symptoms in some patients but produces inconsistent results in others. Paradoxically, some dystonia patients respond to dopamine-blocking drugs, such as tetrabenazine, rather than dopamine-boosting drugs. A new study may help explain why this occurs.



A study led by DMRF grant recipient and former member of the Medical & Scientific Advisory Council Antonio Pisani, MD, PhD of University of Rome Tor Vergata offers new insights into the role of dopamine in DYT1 dystonia. The work of Dr. Pisani and his group highlight the role of RGS9-2, a protein that regulates dopamine signaling in the striatum, part of the basal ganglia in the brain. The researchers have shown that activating RGS9-2 may potentially correct the dopamine imbalance in the brain associated with dystonia and other movement disorders. The results from this study suggest the RGS9-2 protein could be an important therapeutic target for dystonia.



DMRF SCIENCE HIGHLIGHTS

New discoveries about dystonia are published daily as investigators all over the world continue to work toward better therapies and a cure. Here are just a handful of scientific achievements made possible by DMRF's efforts.

- \$35M invested in dystonia science
- First-ever dystonia medical and research centers established
- \$14M for dystonia investigators liberated from Department of Defense
- 250+ investigators funded
- Genes discovered: DYT1/TOR1A, DYT6/THAPI, DYT25/GNAL and others
- First children born with 0% risk of DYT1 dystonia
- Thousands of drug compounds tested
- Dystonia protein structures solved: TorsinA and LULL1
- 28 clinicians trained to treat patients
- Origins of dystonia in brain clarified
- Role of TorsinA protein clarified
- Dystonia models created and shared
- Clinical definition and classification published for physician awareness (twice)
- 6 International Dystonia Symposia for clinicians and researchers
- 5,300+ Patients enrolled in Global Dystonia Registry
- \$1.5M in Dystonia Coalition admin costs saved, funds put toward research

Experts will Gather for 6th International Dystonia Symposium in 2020

The DMRF, in partnership with Dystonia Europe, is proud to announce the Samuel Belzberg 6th International Dystonia Symposium, a research conference to take place June 4–6, 2020 in Dublin, Ireland. The meeting is named in memory of the late Samuel Belzberg, Co-Founder of the DMRF and tireless champion of a global approach to advancing dystonia research and funding a cure. Co-Chairs are H. A. “Buz” Jinnah, MD, PhD of Emory University School of Medicine and Antonio Pisani, MD, PhD of University of Rome Tor Vergata. The program is designed a comprehensive overview of scientific advances in the field and stimulate discussion within and across disciplines. The International Dystonia Symposium is the seminal international dystonia meeting for investigators and clinicians, dating back to 1975. *More information is available at internationaldystoniasymposium.org*

Barbara Oliver Memorial Dystonia Research Fund Supports Investigations into Disabling Childhood Dystonia

The DMRF's latest post-doctoral research fellowship awards focus on understanding the role of TorsinA in DYT1 childhood onset dystonia. Many thanks to Ron Oliver and family for their generous support. Mr. Oliver partnered with DMRF to create the Barbara Oliver Memorial Dystonia Research Award in memory of his late wife who lived with cervical dystonia for many years.

In 1997, DMRF-funded researchers discovered that a subtle error in the DYT1 gene was responsible for a severe type of childhood dystonia. The genetic error causes a protein in the brain called TorsinA to function abnormally.

Barbara Oliver Memorial Dystonia Research Award

Investigator: Gabriela Huelgas-Morales, PhD,
University of Minnesota

Mentor: David Greenstein, PhD

Project: Using the Nematode *Caenorhabditis elegans* to Identify Candidate Substrates for OOC-5/TorsinA

Investigator: Anthony Rampello, PhD, Yale University

Mentor: Christian Schlieker, PhD

Project: A Genetic Approach towards Identifying Torsin Function in Relation to DYT1 Dystonia

KMT2B Emerging as Significant Cause for Childhood Dystonia

AT A GLANCE

- The KMT2B gene may account for 10-30% of non-DYT1 childhood onset dystonia.
- Patients with KMT2B dystonia respond dramatically to deep brain stimulation therapy.

A recently discovered gene called KMT2B (DYT28), though rare, may account for 10–30% of cases of non-DYT1 childhood onset dystonia. KMT2B dystonia is a complex movement disorder with onset typically between 1 and 10 years of age. Most patients initially develop dystonia in a leg or foot, and symptoms progress to affect the arms, face, neck, throat, and voice.

Additional movement symptoms can include tremor and myoclonus. Children may present intellectual disability, psychiatric disorders, subtle facial characteristics, and other non-motor symptoms.

A very significant observation is that although this particular dystonia does not appear to respond well to treatment with oral medications, reduction of motor symptoms after deep brain stimulation surgery can be dramatic. Discoveries surrounding this gene reinforce that proper diagnosis, including comprehensive genetic testing, is necessary to achieve the most effective therapeutic treatment, especially dystonia that develops in childhood.

Myoclonus-Dystonia Research Program

The Myoclonus-Dystonia Research Program is a partnership between the DMRF and the Brown Family Foundation focused on advancing knowledge of this inherited movement disorder. Numerous clinical studies are ongoing:

- An international study to assess non-motor symptoms and quality of life with a standardized questionnaire.
- A retrospective study to compare efficacy of deep brain stimulation in patients in Europe and the USA.
- Exploring altered sense of agency as a common mechanism across different types of dystonia by investigating myoclonus-dystonia patients.
- Role of serotonin in non-motor symptoms.
- A patient registry to support ongoing and future myoclonus-dystonia research.
- Repository for biological samples obtained from myoclonus-dystonia patients.

