



DYSTONIA
MEDICAL
RESEARCH
FOUNDATION

Promise & Progress

SCIENCE REPORT OF THE DYSTONIA MEDICAL RESEARCH FOUNDATION 2016



Dr. Warren Grill presented at the annual MSAC meeting.

Step by Step toward the Cure **DMRF Experts Blaze Trail toward New Discoveries**

The goal of the DMRF's science program is to stimulate medical advancements toward a cure for every individual and family impacted by dystonia. Decades of research have greatly improved knowledge of dystonia, leading to an expansion of treatment options. As medical advancements continue, patients have greater opportunities to feel and function better—this is the ultimate measure of the DMRF's success.

At the annual meeting of the Medical & Scientific Advisory Council (MSAC) on February 25–26, 2016, Scientific Director Mahlon R. DeLong, MD and Chief Scientific Officer Jan Teller, MA, PhD invited attendees to discuss and recommend scientific priorities for the coming year. Keynote speaker was Warren Grill, PhD, Addy Family Professor of Biomedical Engineering at Duke University. Fellow presenters included new MSAC members Thomas Schwartz, PhD, Professor of Biology at Massachusetts Institute of Technology, and Kristina Simonyan, MD, PhD, Associate Professor Neurology and Otolaryngology at Mount Sinai School of Medicine. Read about Dr. Simonyan's exciting new discoveries on page 2.

H. A. Jinnah, MD, PhD, Professor of Neurology, Human Genetics & Pediatrics at Emory Healthcare and Director of the Dystonia Coalition, and Beth-Anne Sieber, PhD, Program Director for dystonia at the National Institute of Neurological Disorders & Stroke, also provided updates.

UPDATE: Myoclonus-Dystonia Research Program

The DMRF manages a special program to stimulate research into myoclonus-dystonia supported by the Brown Family Foundation. Myoclonus-dystonia is an inherited movement disorder characterized by a combination of rapid, jerking muscle contractions (myoclonus) and sustained twisting and repetitive movements (dystonia). Although relatively rare, research on myoclonus-dystonia is revealing insights that may be applicable to the mechanism and genetics of all inherited dystonias. Experts from around the globe convened at the most recent Myoclonus-Dystonia Workshop, February 18–19, 2016. Two new myoclonus-dystonia grants are planned for 2016.

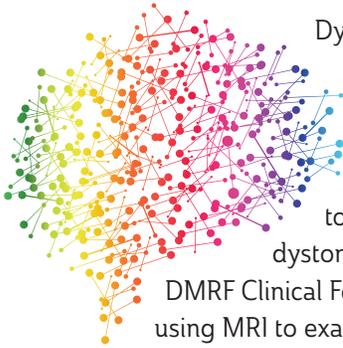
DMRF Creates New Award for Young Investigators



Mark Moehle, PhD has earned the very first Mahlon DeLong Young Investigator Award. He is a postdoctoral research fellow at the Vanderbilt Center for Neuroscience Drug Discovery. Dr. Moehle received the \$55,000 award for a project entitled, "Muscarinic Receptor M4 Modulation of Dopaminergic Signaling in a GNAL Dystonia Mutant Mouse Model." The project seeks to understand how a mutation in the DYT25/GNAL gene leads to dystonia with a particular focus on neurotransmitter interactions in neurons. In addition to providing key data in determining how mutations in GNAL lead to dystonia, these studies will provide pre-clinical efficacy data on the use of M4 antagonist drugs to treat dystonia.

GETTING (RE)ORGANIZED

Abnormal Brain Pathways in Adult Onset Dystonia



Dystonia is a circuit disorder of the brain involving the basal ganglia, cerebellum, and the cortex. Medical & Scientific Advisory Council Member Kristina Simonyan, MD, PhD led two recently published studies describing important advancements in our understanding of how these networks are compromised in adult onset focal dystonia. These studies suggest a common underlying mechanism to dystonia as well as unique mechanisms specific to particular subtypes.

DMRF Clinical Fellow Pichet Termsarasab, MD contributed to this work. In a study using MRI to examine volunteers with spasmodic dysphonia, writer's cramp/hand dystonia, cervical dystonia, and blepharospasm, investigators found patterns of brain activity that were very different from healthy controls. They discovered re-organized brain circuits across all dystonias, and unique changes in task-specific dystonias.

The investigators took a closer look at spasmodic dysphonia (SD) to further explore functional brain circuits. Differences in how the brain processes sensory information have long been associated with dystonia, but it is unknown how these differences correspond to the various subtypes of dystonia. Dr. Simonyan and team looked at subtypes of SD: adductor and abductor as well as sporadic cases and cases with a family history of SD. Volunteers were asked to respond to visual and tactile stimuli (for example, flashing lights and blindfolded touch to the hands). MRI was used to monitor brain activity during these sensory exercises. The investigators found similarities and differences among the SD subtypes in terms of how affected subjects processed sensory information compared to controls. Certain abnormalities in how volunteers responded to stimuli across time were found in all SD subtypes, and especially in patients with a family history of SD. Patients with familial SD had greater involvement of the cerebellum during these exercises, while patients with sporadic SD displayed greater involvement of other brain areas. There were differences among volunteers with adductor and abductor SD.

AT A GLANCE

- Brain pathways are circuits of neurons (brain cells) that conduct signals from one part of the nervous system to another.
- Dystonia patients process sensory information using different brain pathways than healthy controls.
- The coordination of signals between certain areas of the brain is compromised in adult onset focal dystonia.
- Identifying these disorganized brain pathways may provide opportunities to develop treatment strategies to correct them.

Consider Registering as a Brain Donor. Learn more at dystonia-foundation.org/brain



Dystonia in Four-Legged Friends

Several hyperkinetic movement disorders described in dogs and livestock show similarities to human movement disorders, especially paroxysmal dystonia and dyskinesias.

A team of investigators partially supported by the DMRF recently published a report exploring the possibilities that distinct neurological movement disorders in domestic animals represent dystonia. The hope is that animals may help investigators advance our understanding of human dystonia.

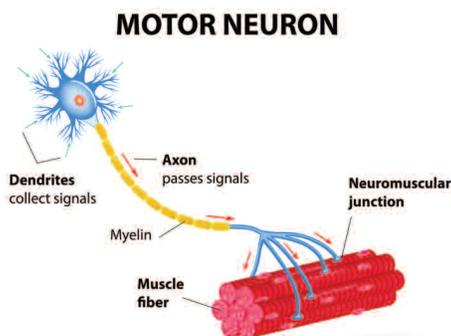
The study describes a number of case reports, including a Great Dane dog with severe blepharospasm aggravated by stress and bright light. The spasms progressed to permanent closure of the eyelids. EMG revealed overactivity of the orbicularis oculi muscle, the same muscle involved in human

blepharospasm. Botulinum neurotoxin injections finally relieved the symptoms.

Episodic falling in Cavalier King Charles Spaniels is an inherited disorder that shares similarities with human paroxysmal dyskinesias. In affected dogs, exercise and excitement trigger episodes of abnormal gait and falling that can last several minutes. There may be sustained extension of the limbs and back arching. The dogs do not lose consciousness. A genetic mutation has been identified, but how the mutation leads to symptoms is unknown.

It has yet to be verified whether these and other movement disorders in domestic animals represent dystonia, but future study may help clarify.

TorsinA May Have Critical Role in Health of Basal Ganglia Neurons



AT A GLANCE

- TorsinA is a protein found in neurons (brain cells).
- DMRF-funded investigators made groundbreaking connections between impaired TorsinA function, brain circuits, and dystonia symptoms.
- Abnormal TorsinA has been linked to temporary neuron loss in mice.
- Normal TorsinA appears critical for the survival of these neurons.

Not long ago, a team of researchers led by DMRF Stanley Fahn Award Recipient William Dauer, MD, Associate Professor of Neurology at University of Michigan, published a remarkable study linking dystonia symptoms in mice to a loss of neurons in certain brain structures and abnormalities in a cellular protein called TorsinA. This is a departure from the widespread observation that isolated (primary) dystonia is not characterized by structural changes in the brain. In the continuation of this work, researchers have made further discoveries regarding the origins of dystonia in the nervous system.

Dystonia symptoms originate in part from problems in an area of the brain called the striatum (part of the basal ganglia). The striatum is made up of different types of neurons, but it remains unclear which of these are susceptible to degeneration in dystonia.

The investigators discovered that deleting the gene for TorsinA from certain neurons in mice (including in the striatum) causes abnormal twisting movements. The mice developed symptoms at a stage of brain development equivalent to the typical human age of onset. The movements were suppressed with anticholinergic medications, which are commonly used to treat human patients. The investigators analyzed brain tissue from the mice and found that the twisting movements began at the same time that a type of neuron in the striatum called cholinergic interneurons degenerated. Postmortem studies of dystonia patients have also revealed abnormalities in these neurons.

The neuron loss seen in the mice occurs only in specific brain structures involved in movement control and only for a period of time that coincides with the onset of symptoms.

These findings challenge the notion that dystonia occurs in a structurally normal nervous system and suggest that cholinergic interneurons in the striatum require TorsinA to survive. The next challenge is to identify what causes the targeted loss of cholinergic interneurons and to investigate how this cell loss affects the striatum.

Partners in the Pharmaceutical Industry

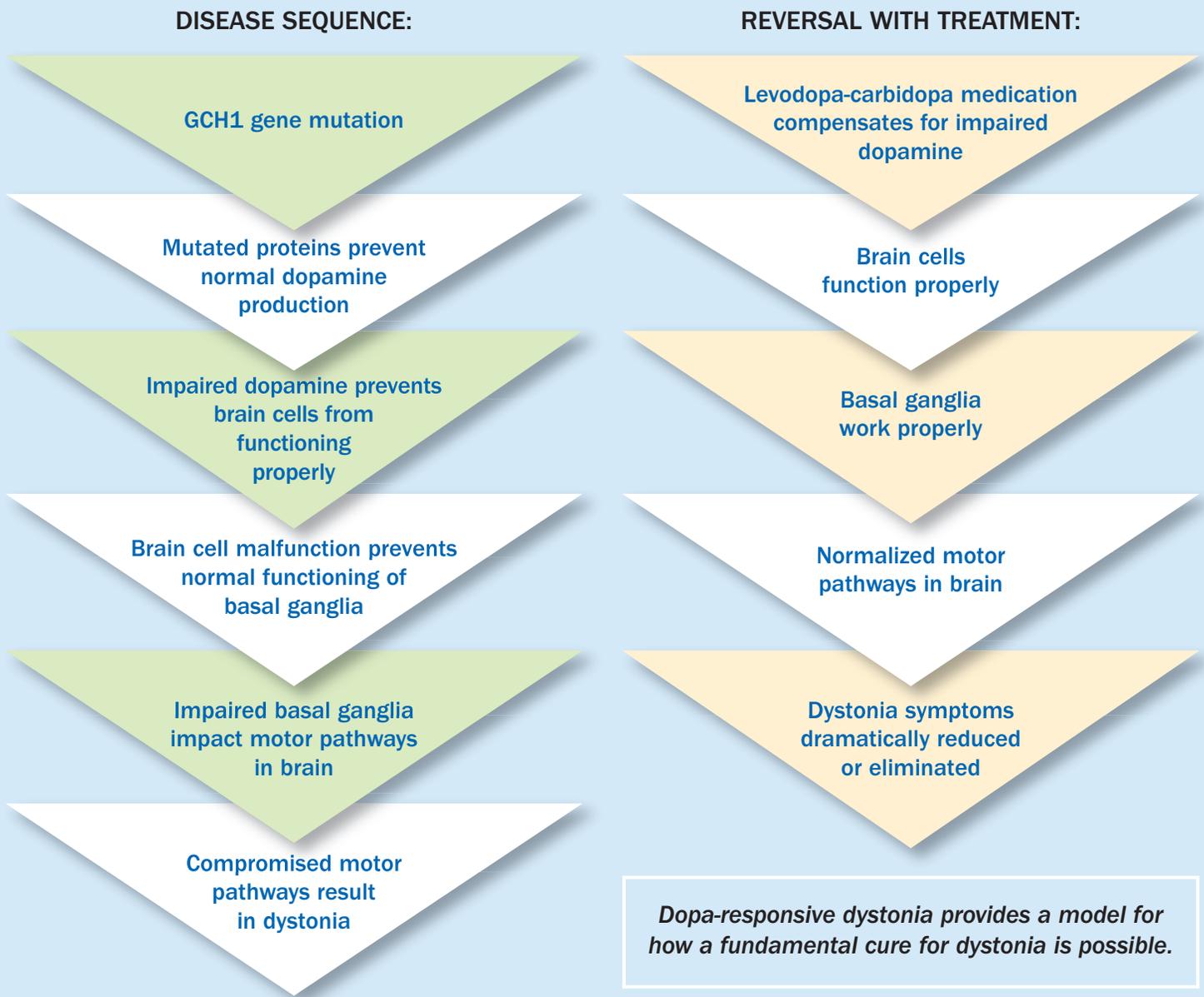


As part of a comprehensive approach to accelerating the availability of new and improved dystonia therapies, the DMRF is continually pursuing opportunities to engage the pharmaceutical industry. Because negotiations with pharma involve confidential information and proprietary interests, the DMRF is often unable to publicize these efforts. Such partnerships may involve contracts for joint projects and/or conducting clinical trials.

For example, through a multi-year collaboration with BioFocus DPI, the DMRF has identified a number of potential dystonia drug targets. By taking advantage of high throughput screening and robotic automation technology, more than 300 prospects were identified from 4,500 candidates. The DMRF is currently negotiating a contract with an international team of investigators to explore the next phase of this work. Efforts to exploit other promising targets will continue.

Moving toward a Cure: Lessons from DRD

A subtype of dopa-responsive dystonia (DRD) is the only dystonia disorder in which the underlying disease mechanism is fully understood, and treatment targets the biochemical origins of the disorder.



Share your dystonia experiences with researchers searching for a cure. Join the Global Dystonia Registry: globaldystoniaregistry.org



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