



## The Pediatric Neuromuscular Service: Coordinated, multidisciplinary care for children with neuromuscular disorders

Although the gene for Duchenne muscular dystrophy (DMD) was discovered more than 20 years ago, the treatment of children with this progressive, invariably fatal disease has unfortunately improved relatively little since that time. Committed to improving and extending the lives of children with DMD and other neuromuscular disorders, last year MGHfC announced the creation of the Pediatric Neuromuscular Service.

Under the leadership of director Brian Tseng, MD, PhD, the service conducts cutting-edge research and provides comprehensive, multidisciplinary diagnosis, treatment, and follow-up care for children with more than 40 neuromuscular disorders, including:

- Duchenne muscular dystrophy/Becker muscular dystrophy
- myopathies
- peripheral neuropathies, including Charcot-Marie-Tooth disease
- other pediatric neuromuscular weakness

### Coordinated, multidisciplinary care

The foundation of the Pediatric Neuromuscular Service is its highly coordinated, multidisciplinary approach to care, which is essential to achieving the best possible outcomes for children with neuromuscular



Brian Tseng, MD, PhD, director of the Pediatric Neuromuscular Service, with a patient and Physical Therapist, Elise Townsend, PT.

disorders. The service includes the following specialties and specialists, who collaborate on each patient's care plan:

**Pediatric neurology:** Brian Tseng, MD, PhD, Ann M. Neumeyer, MD, Cindy Kane, RN, Laurie Bliss, Clinic Coordinator

**Pediatric endocrinology:** Paul A. Boepple, MD

**Genetics:** Marsha F. Browning, MD, MPH, Christa Haun, CGC

**Pediatric pulmonology:** Bernard T. Kinane, MD, Craig Canapari, MD (sleep disorders), Pat Costello, RT

**Pediatric cardiology:** Ana Maria Rosales, MD

**Social work:** Amy Krasner, MSW

**Physical therapy:** Elise Townsend, PT, DPT, PhD

**Orthotics:** Gordon M. Craig, CO/CPO

**Rehabilitation technology:** Ian Kingscote, RTS

**Nutrition:** Alexa Schmitt, RD, LDN

**Palliative Care:** Pat O'Malley, MD, Sandra Clancy, PhD

### Single-day evaluation

For the benefit of patients and families, many of whom travel long distances to be seen, initial evaluations (including overnight sleep studies) with all the appropriate specialists are scheduled on a single day during the weekly clinic. To facilitate this visit, families are offered the services of an "appointment buddy," a hospital volunteer who, among many other personalized services, escorts them to appointments.

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**When children reach adulthood, they may be smoothly transitioned to Mass General's adult neuromuscular service.**

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## Researchers Provide First Evidence for a Gene That Influences Anxiety: Discovery suggests new therapeutic target for disorders affecting three in ten Americans

As recently as 50 years ago, it was widely believed that the root cause of most psychiatric disorders was the patient's early environment. Reflecting the attitude of the day is this statement in 1953 by psychoanalyst John N. Rosen, MD, who wrote, "Schizophrenia... is caused by the mother's inability to love her child."

Today, a lot has changed. Based on a growing body of research, much of which is being conducted at Massachusetts General Hospital, it is largely accepted by the mental health community that while environment plays an important role in the development of psychiatric disorders — many of which begin in childhood — genetic factors also have a significant impact (*see chart, right*). Just as with many medical conditions, whether someone develops a psychiatric condition and how debilitating it will be is the result not of nature *or* nurture, but rather a complex interplay of both.

A case in point is recent research conducted by Mass General investigators, in collaboration with scientists at Yale University and the University of California at San Diego, which provided the first evidence that a gene known to influence anxiety in mice also influences anxiety proneness in humans. This finding was published in the March 2008 issue of the *Archives of General Psychiatry*. Jordan W. Smoller, MD, ScD, of the

Familial and Genetic Risks for Psychiatric Disorders <i>Courtesy: Jordan W. Smoller, MD, ScD</i>		
Disorder	Familial Relative Risk	Heritability*
Autism	75	>90%
Schizophrenia	10	85%
Bipolar disorder	7-10	85%
ADHD	2-6	77%
Alcohol/drug addiction	3-8	55%
Eating disorders	10	55%
Depression	3	40%
Anxiety disorders	5	40%

\*Heritability is the proportion of phenotypic variance in a population attributable to genetic factors.

Mass General Department of Psychiatry, was the lead author. Others at Mass General who participated in this research were Joseph Biederman, MD, Jerrold Rosenbaum, MD, and Dina Hirshfield-Becker, PhD.

Often beginning in childhood, anxiety disorders —, which include social anxiety disorder, phobias, and obsessive compulsive disorder —, are the most common psychiatric condition. Pharmacologic and psychosocial therapies help some patients, but these are sometimes inadequate, spurring researchers to search for new therapies.

In the study, which involved children from 119 families and nearly 800 unrelated adults, researchers found that variations in the gene *RGS2* were associated with three well-validated phenotypes for anxiety disorders. These are: childhood temperament (specifically behavioral inhibition, which is characterized by fear or avoidance of novel situations); introversion in adults, a core personality trait in social anxiety disorder; and increased limbic activation during emotion processing, as assessed by neuro-imaging studies.

*RGS2* was a logical candidate for scrutiny because mice, in which *RGS2* is knocked out, exhibit fear/avoidance behavior. Moreover, the gene is known to play a key role in mediating receptors of neurotransmitters, such as serotonin and dopamine, that affect anxiety and mood.

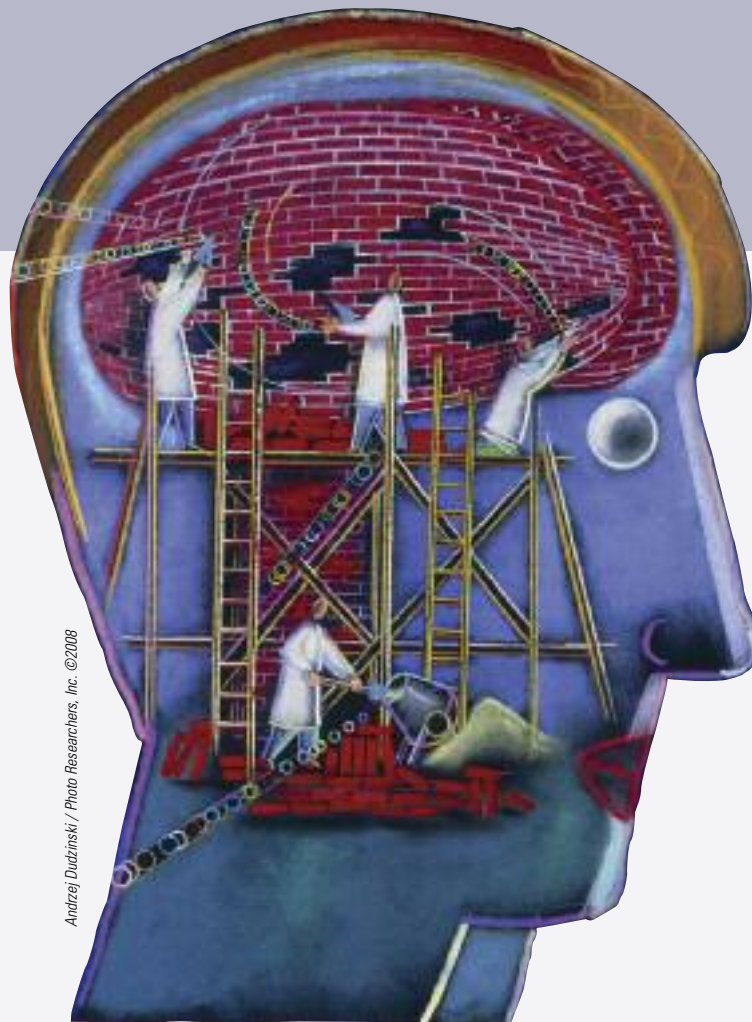


While more studies must be done to pinpoint the gene's role in specific anxiety disorders, the results of this translational research provide further evidence of the genetic influence on anxiety disorders, and suggest a potential therapeutic target that might lead to new, more effective treatment options.

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Dr. Smoller is co-editor with Beth Rosen Sheidley, MS, CGS, and Ming T. Tsuang, MD, PhD, DSc, of *Psychiatric Genetics: Applications in Clinical Practice* (American Psychiatric Publishing, Inc. 2008). Written for clinicians who may not have particular expertise in genetics, this resource provides a primer on psychiatric genetics and information on how to apply psychiatric genetic knowledge in everyday practice.

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## Pediatric Traumatic Brain Injury

### Innovative research aims to improve outcomes for TBI patients

Advances in critical care medicine over the past few decades have reduced the mortality rate for children with severe traumatic brain injury (TBI). Yet considerable work remains to be done for TBI survivors. These patients frequently face a long, painful, and costly rehabilitation followed by a lifetime of cognitive and motor deficits, neuropsychiatric disorders, and increased risk of neurologic disorders.

According to MGHFC critical care specialist Michael J. Whalen, MD, much of the damage caused by TBI is not the direct result of initial trauma to the brain, as was formerly believed. Rather, it is caused by secondary brain injuries resulting from a cascade of complex events that occur over days to months, and affect regions of the brain well beyond the initial site of injury.

The outcomes of patients with severe TBI are influenced by many factors and are virtually impossible to predict. Yet it is becoming increasingly clear that patients' genes play a significant role in how they will fare over time.

With the goal of improving the outcomes of pediatric TBI patients, Dr. Whalen and his colleagues at Mass General's Neuroscience Center are conducting research aimed at identifying the genes that affect TBI outcomes; elucidating the mechanisms of secondary brain injury; and, based on those discoveries, finding new therapeutic targets and evaluating innovative therapies using immature animal models of TBI.



*MGHfC critical care specialist Michael J. Whalen, MD, is conducting research aimed at better understanding and finding new treatments for traumatic brain injury.*

## Targeted pharmacologic agents

In previous studies, MGHfC researchers found that the dual inhibition of tumor necrosis factor-alpha (TNF- $\alpha$ ) and Fas, which are induced at TBI, reduce brain tissue damage, motor dysfunction and spatial learning deficits in mice. They are now searching the TNF- $\alpha$ /Fas pathway for downstream mechanisms — which might have greater specificity and a longer therapeutic window — as potential therapeutic targets.

Building on this work, Dr. Whalen and his collaborators, Junying Yuan, PhD, of Harvard Medical School and Alexei Degtarev, PhD, of Tufts University, are currently evaluating a novel agent in a novel class of agents — necrostatin-1 — in mouse models of TBI. Necrostatin-1 targets a new, regulated cell-death pathway, called necroptosis, that recent studies have shown occurs in TBI and stroke. Thus far, the drug has shown striking effects in pediatric and adult mouse TBI models, including reducing tissue damage and improving motor and cognitive function.

Another gene of interest is ApoE4, which affects beta amyloid production. Mice with the ApoE4 mutation have a higher incidence of poor outcomes after TBI. Dr. Whalen and his team, along with collaborators Giuseppina Tesco, MD, PhD (MassGeneral Institute for Neurodegenerative Disease), and Rebekah Mannix, MD (Children's Hospital Boston), are now investigating whether mice with this gene variant produce more beta amyloid. If so, they



**Michael R. Hamblin, PhD, with a mouse model of TBI undergoing low-level laser therapy, a potential non-invasive treatment for TBI.**

plan to evaluate whether BACE inhibitors might improve motor and cognitive sequelae of mouse models of TBI.

## Low-level laser therapy: a potential noninvasive option

In a collaborative effort, Dr. Whalen and Michael R. Hamblin, PhD, of Mass General's Wellman Center for Photomedicine, are pursuing an innovative approach to neuroprotection following TBI using low-level laser therapy (LLLT). A non-invasive therapy applied transcranially, LLLT has been used successfully by researchers elsewhere in a mouse model of TBI.

If LLLT is effective for TBI treatment, as the collaborators hypothesize, it would become the first therapy to improve cognitive, neuropsychiatric and motor function in TBI patients. In addition to being a noninvasive, safe, and ambulatory therapy, LLLT could also be used in the chronic management of TBI, offering new hope to patients well after their initial injury.

**For more information or to refer a patient, please call the MassGeneral Hospital for Children Access and New Appointment Center: 888-MGHfC-11 (888-644-3211).**

## Pediatric Neuromuscular Service

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The results of each patient's evaluation are communicated promptly to the family and referring primary care physician. Depending on the diagnosis and treatment plan, patients may be seen in clinic once or twice a year; every effort is made to coordinate as many services as possible in the child's local community. When children reach adulthood, they may be smoothly transitioned to Mass General's adult neuromuscular service.

## Bench-to-bedside research

The Pediatric Neuromuscular Service also conducts research focused on improving treatments for children with muscular dystrophy.

One area of investigation in Dr. Tseng's lab involves an animal model of DMD, the mdx mouse. Although it lacks the dystrophin protein, the mdx mouse does not exhibit the severe effects of the disease seen in humans. Dr. Tseng and his research team are making significant progress on elucidating the compensatory mechanisms of mdx mice, which suggest new targets for therapies aimed at slowing the progression of DMD.

Other research is focused on using screening technologies to evaluate compounds for improved treatment of muscular dystrophy. The goal of this work is to identify the most effective compounds and determine the optimal doses with the fewest side effects.

**For more information or to contact a Pediatric Neuromuscular Service clinician directly, please call the MassGeneral Hospital for Children Access and New Appointment Center: 888-MGHfC-11 (888-644-3211). Or visit [massgeneralforchildren.org](http://massgeneralforchildren.org).**



**Orthotist Gordon M. Craig, CO/CPO, is a member of a multidisciplinary team dedicated to caring for patients with neuromuscular disorders.**

## Autism Treatment Network Receives \$12 Million Grant

MGHfC-led grant will fund clinical research and development of evidence-based guidelines

MGHfC recently received a three-year, \$12 million grant from the Health Resources and Services Administration (HRSA) to develop a multi-site research network to address physical health conditions among children with autism spectrum disorders. The network will be built on the Autism Treatment Network (ATN), which receives its core funding from Autism Speaks, the nation's largest autism advocacy organization.

The ATN is a collaboration that includes 15 participating ATN centers nationwide, including MGHfC. The grant will be led by the ATN Clinical Coordinating Center at MGHfC under the leadership of the center's director and lead principal investigator, James M. Perrin, MD, who is also director of the MGHfC Center for Child and Adolescent Health Policy.

"With this funding, the ATN will develop and conduct research projects focused on interventions that have a direct impact on improving the physical health and well-being of children and adolescents with autism," says Dr. Perrin. The grant also expands the ATN's ongoing efforts to develop evidence-based clinical guidelines.

Specifically, the HRSA funding will support two research projects that address issues of great concern to parents: sleep and nutrition. The sleep study, led by Beth Malow, MD, of Vanderbilt University, will develop and evaluate a parent-based sleep-education program aimed at improving sleep and behavioral outcomes.

The nutrition study, led by University of Rochester investigator Susan Hyman, MD, will evaluate nutritional intake and diet patterns and their relationship to gastrointestinal and sleep conditions in children with autism.

**For more information, please contact James M. Perrin, MD, Director of the MGHfC Center for Child and Adolescent Health Policy, at [jperrin@partners.org](mailto:jperrin@partners.org).**

"With this funding, the Autism Treatment Network will develop and conduct research projects focused on interventions that have a direct impact on improving the physical health and well-being of children and adolescents with autism."

— James M. Perrin, MD, MGHfC Center for Child and Adolescent Health Policy



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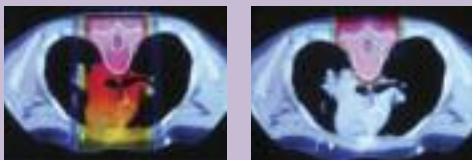
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**Isodose depictions for photon (left) and proton (right) craniospinal radiation therapy. The proton technique spares significant radiation to the esophagus, bronchi, lungs and heart.**

*Writing: Bennett Medical Communications*

Introducing the Pediatric  
Neuromuscular Service  
First Evidence for Anxiety-  
Influencing Gene  
Pediatric Traumatic  
Brain Injury  
Autism Treatment Network  
Receives \$12 Million Grant

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