

Channeling In

The Newsletter of the IDEA League

Sodium Channel Dysfunction: Studies of Dravet Syndrome Using Mouse Models

By Michelle Welborn, PharmD

This article focuses on the works of Dr. Bill Catterall, Chair of Pharmacology, University of Washington School of Medicine.

We are learning more about the disease processes associated with Dravet syndrome as more patients are diagnosed with the disorder; however the complex cellular mechanisms involved are not fully understood. Recent discoveries by Bill Catterall, PhD and his colleagues at the University of Washington bring us a step closer to understanding the physiochemical mechanisms associated with genetically

distinct epilepsy syndromes involving the sodium channel.



Sodium channels are critical regulators of neuronal excitability. De novo loss of function mutations in the SCN1A gene potentially lead to haploinsufficiency of Nav1.1 channels. *Theoretically*, haploinsufficiency of the Nav1.1 channel should not cause epilepsy because

reduced sodium current produces neuronal inexcitability rather than the hyperexcitability that is associated with seizure activity.

Dr. Catterall has generated mouse models of Dravet syndrome by ablating the SCN1A gene in mice and has shown that dramatic loss of sodium current in the hippocampal GABAergic inhibitory neurons in these mice may cause their epilepsy. Upregulation, which is a protective mechanism that allows more neurons to be generated during a loss, is not sufficient to produce

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Encouraging Words From Our President

By Joan Skluzacek

I was sitting here at my computer, with a blank Word document open on the screen, trying to decide what to write about for this issue's *Encouraging Words* when Nick, in his innocent wisdom, provided me with the inspiration I needed. He approached silently from behind and put his hand on my arm. I turned to find him smiling brilliantly into my eyes. When I smiled back, his eyes began to sparkle and he tipped his head for a kiss on the forehead. He sat on my lap and put his fingertips on my mouth. He wanted me to sing him a song, so I burst into one of his favorites, *You Are My Sunshine*, after which he collapsed into giggles (I'm

sure it was my singing!) and demanded another kiss on the forehead...and another, and another...until he and I were both laughing so hard we could hardly breathe.

When we had both caught our breath, Nick stood and pulled on my hand until I turned my back on my computer and followed. He led me out the door and to the car. He wanted to go joyriding – one of his very favorite things to do. So we hopped in the car and drove around watching the world go by. I sang more songs while Nick clapped his accompaniment. Of course, the best joyrides end with a stop at Dairy Queen for a Banana Cream Pie Blizzard

ice cream treat. We sat in the grass enjoying our treats and throwing a ball for Ruby to chase. After that, this column practically wrote itself.

In a recent forum post, our friend Rita gently reminded us all of the importance of playtime with our kids. I think it may even be critical for our survival. So if things seem quiet on my end, hopefully it will be because I have set aside my research, phone calling, letter writing, and such and I'm with Nick, drawing rainbows on the back patio with sidewalk chalk. This may not have been the trip of our dreams, but we can still enjoy the destination.

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Our IDEAL is a Cure



It is well understood that cognitive impairments are characteristic of Dravet syndrome, however there is much to be learned about the nature and spectrum of those impairments.

Scientific Update

Co-Morbid Conditions:

Understanding Dravet Syndrome as a Systemic Disorder Requiring Coordinated Multi-Disciplinary Care, *part 2*

By Joan Skluzacek

In our previous issue, part 1 of this article described some of the co-morbid conditions found in significant numbers of children with Dravet syndrome as reported by Joan Skluzacek, president and executive director of the IDEA League and Dr. Beverly Wical, pediatric neurologist at Gillette Children’s Specialty Healthcare and member of the IDEA League professional advisory board in their abstract, Dravet Syndrome: Expanding the Clinical Spectrum, which they presented at the annual meeting of the American Epilepsy Society in San Diego, California. Part 2 will describe developmental disorders found in significant numbers of children with Dravet syndrome.

It is well understood that cognitive impairments are characteristic of Dravet syndrome, however there is much to be learned about the nature and spectrum of those impairments. In 2005, parents of 57 children in an international online support group responded to survey questions about the development of their children with a clinical diagnosis of Dravet syndrome. Participation was voluntary. Questions were chosen by group leaders to investigate the numbers of children affected by problems that were frequently discussed in the forum.

One hundred percent of the survey participants reported that their children had developmental delays. The parents of 56 children responded to questions about the severity of their children’s cognitive impairments. Thirty-

nine percent (22/56) reported severe to profound cognitive impairment, 29% (16/56) reported moderate to severe cognitive impairment, and 30% (17/56) reported mild to moderate cognitive impairment. A correlation was noted between the frequency and severity of status episodes and developmental progress. Of those reporting mild to moderate impairments, 65% to 71% had experienced the lowest frequency and severity of status episodes. This was more significant than the age of onset.

Parents of 44 children responded to survey questions about autism spectrum characteristics in their kids. Seventy-eight percent (33/44) had concerns about autism spectrum disorder. About one fourth of these respondents reported that their children had been “diagnosed with autism”, about half reported observing autistic traits in their children, and about one-fourth reported having concerns that their child may have autistic traits, but were unsure. Ninety-eight percent (43/44) of these parents reported *behavioral concerns* about unusual activity including: lack of reserve with strangers, perseverative/ repetitive behaviors, self-stimulation (ie. hand flapping), excessive affection, echolalia, and preferring to play alone – ignoring group activities. Sixty-eight percent (29/44) of these parents reported *sensory integration concerns*. Of these, 65% (20/29) reported visual sensitivity, especially sensitivity to ambient light and to patterns, where exposure may trigger seizures. Tactile defensiveness was reported

by 39% and 30% reported auditory sensory integration impairment.

Communication disorder is one of the hallmark characteristics of autism spectrum disorders. The parents of 57 children responded to surveys regarding *communication*. All 57 (100%) reported communication disorder. Of these, 40% were severe language delays, 17% were moderate, and 21% reported mild delays. Twenty-one percent reported that early language development was normal, followed by the loss of language skills as the disorder progressed.

In addition to growth and nutritional assessment, evaluation of immune function, orthopedic assessment, and sleep evaluation, interdisciplinary coordinated care of children with Dravet syndrome should include regular global developmental assessments beginning as early as possible. Early implementation of speech, occupational, physical, and social/play therapies in an enriched environment can improve the outcome.

Finding Resources for Our Children

By Mary Anne Meskis

Dravet syndrome is not simply a seizure disorder, but rather a neurodevelopmental disorder earmarked by varying seizure types, developmental delays and several co-morbid conditions that warrant attention and therapies from an early age. Those of us caring for a child with Ds often feel there is never enough time, energy or finances to address that child's special needs. This is part one in a series of articles to help families find resources available to them. We will draw on the experiences of families from around the world. In this issue I offer a brief overview of some of the services available in the United States.

The federal *Individuals with Disabilities Education Act* (IDEA) authorizes early intervention for young children up to age three. Services include family training and counseling as well as physical, speech and occupational therapies. Children above age three receive their special education services through the local school district.

Supplemental Security Income (SSI) provides monthly cash benefits to children with severe disabilities. Children must meet strict requirements based on income eligibility and the SSI definition of

disability. For application forms or more information, visit their website at www.ssa.gov.

Medicaid and the *State Children's Health Insurance Program* can cover diagnostic, treatment and rehabilitative services. These services can help offset the out-of-pocket expenses incurred by the family. Visit your state's website and check for programs and services available for disabled children.

The goal of *Home and Community-Based Waiver services* is to provide services to persons at home to avoid placing them in a hospital or nursing facility. These waivers can be used to access Medicaid services not normally available, including case management, health aides, habilitation, and respite services. Although this is a federal program, states are allowed to determine their criteria and eligibility for administering the program. Many states offer a limited number of waiver slots and there may be a waiting list for services. Check your state's website for more information.

If you are not eligible for *respite care* through any of the above programs, I would recommend visiting the United Cerebral Palsy website at

www.ucp.org. They offer respite care at no cost to any child with developmental disabilities, not only those with CP. Contact your local UCP office for more information. Please note that some areas do have a waiting list.

Contact the *social worker* at your local hospital for suggestions on programs and services. They will know what is available locally and what your child may qualify for.

Your child may qualify for *grants* that offer funds for the cost of durable medical goods and therapies. Each organization will set its own criteria for who will qualify. These grants are most often based on income. However, there are some non-profit organizations that offer grants to middle-class families who are unable to qualify for other services.

Next in our series will be an article by Dina Nelson. Dina is an incredible advocate for her daughters, Sydney and Sadie and is extremely knowledgeable on this subject. If you have information about resources in your region that you would be willing to share, please contact us at newsletter@idea-league.org.



Those of us caring for a child with Dravet syndrome often feel there is never enough time, energy or finances to address that child's special needs.

Join Us For Our Upcoming Parents' Retreat Weekend

Michelle Welborn, chair of the IDEA League Professional Advisory Board, has generously volunteered to host our next Parents' Retreat Weekend. The gathering will coincide with her second annual *Boogie for Babies* fundraiser and both events will take place in and around lovely Winston-Salem, North Carolina, USA. The retreat will begin with a dinner on the evening of Friday, November 9th and continue through Monday the 12th. The fundraiser will be held on the evening of the 10th. Other planned activities include Sunday brunch and IDEA League meeting, a tour of Old Salem, and time at the Welborn's chalet on Watauga Lake in the beautiful Blue Ridge mountains. To learn more about the retreat or to RSVP, please contact Michelle by email at michelwelborn@yahoo.com. We hope to see you there!



In Loving Memory of Brianna Wilson

By Paula Janfield

I will never be able to hear the theme song to *Dora The Explorer* without thinking of Brianna Wilson. Brianna loved Dora! She had all the accessories, and I could see the adventure in her eyes as she explored through Dora's.

You would never know that Brianna suffered with so many uncontrolled seizures. She smiled so frequently and freely, that you would never realize what an effort it probably took some days. Brianna loved to laugh, and always laughed with you, to make sure you knew that

the two of you shared a special joke together. Her sisters saw this the most, and the bond between the girls was awe-inspiring.

It is really hard to capture the vitality and mischief of a child in print, but I know that all of us can relate to how special and dearly loved this little girl is. It is of some comfort to know that the seizures are no longer racking Brianna's body.

Brianna's vitality and beauty will live forever in the hearts of her family, and in a small way, she will live forever in our

children too.

Brianna is survived by her parents, Dawn & Dale and her sisters, Kaitlyn and Melissa. She will be deeply missed by her family and all the people whose lives she touched in the short time she was with us. May the Wilson Family find some peace through these hard times, and smile frequently upon the beautiful memories Brianna has left. She is exploring alongside Dora now, and I am positive that topmost item in her backpack is the love her family gave her.



Brianna Wilson

November 25, 1999-April 4, 2007

In the Spotlight

By Michelle Welborn, Pharm. D.

This issue we are pleased to introduce you to Dr. William Catterall. Dr. Catterall's current research project is of utmost interest to the IDEA League as it focuses specifically on Dravet syndrome. Using a mouse model, he and his research team will study ion channel genes and proteins in the brain to determine which are changed in this disease and what effects the alterations have. We encourage you to read more about his exciting research in this issue's feature article.

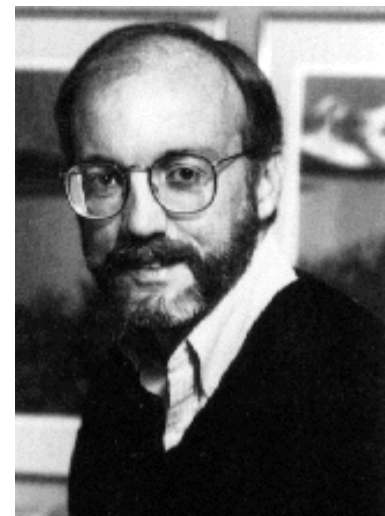
Dr. William Catterall received his B.A. degree in chemistry from Brown University, his Ph.D. in physiological chemistry from Johns Hopkins School of Medicine, and his postdoctoral training in neurobiology and molecular pharmacology as a Muscular Dystrophy Association Research Fellow with Dr. Marshall Nirenberg at the National Institutes of Health. Following a three-year stint as

a staff scientist at the NIH, he joined the faculty of the University of Washington School of Medicine as an associate professor of pharmacology. He went on to become first a full professor and then eventually chair of the department.

After establishing his laboratory at the University of Washington, Dr. Catterall and his colleagues discovered the voltage-gated sodium and calcium channel proteins, which are responsible for generation of electrical signals in the brain, heart, skeletal muscles and other excitable cells. Their subsequent work has contributed much to understanding the structure, function, regulation and molecular pharmacology of these key cell-signaling molecules.

Dr. Catterall's research has been recognized by the Passano Foundation Young Scientist Award, the Jacob Javits Neuroscience

Investigator Award, the Basic Science Prize of the American Heart Association, the Mathilde Soloway Award in Neuroscience from the NIH, the H.B. Van Dyke Award in Pharmacology and the Bristol-Myers Squibb award for distinguished Achievement in Neuroscience Research. He has been elected to the National Academy of Sciences, where he served as Chair of the Section of Physiology & Pharmacology from 1998 to 2001, as well as to the Institute of Medicine and the American Academy of Arts & Sciences. He has served as editor-in-chief of *Molecular Pharmacology*, was a founding member of the editorial board of *Neuron* and has been an editorial board member of several other professional journals. To date, Dr. Catterall's laboratory has published over 300 research papers and 30 reviews on voltage-gated ion channels.



Dr. William Catterall

Dr. Catterall's research is of utmost interest to the IDEA League as it focuses specifically on Dravet syndrome.



The results of experiments with these mouse models suggest that failure of excitability of hippocampal GABAergic inhibitory neurons is a possible cause of intractable epilepsy syndrome.

Mouse Models, *continued from page 1*

enough GABAergic inhibitory neurotransmission to balance the naturally existing excitatory neurotransmitters; therefore, seizures ensue. The results of experiments with these mouse models suggest that failure of excitability of hippocampal GABAergic inhibitory neurons is a possible cause of this intractable epilepsy syndrome. The theory is consistent with the response seen in children with Dravet syndrome to benzodiazepines, including clobazam, clonazepam, diazepam, midazolam, et al. and other antiepileptic drugs that work on GABA receptors in the brain to enhance inhibitory neurotransmission.

Dr. Catterall found that mice with a heterozygous loss of one allele of the Nav1.1 channel gene are ataxic as measured in tests of walking a straight line and walking on a narrow rod. Analysis of the cerebellar Purkinje neurons, which are crucial in coordinating movement, show that there is a dramatic loss of sodium current. The Purkinje neurons are the projection neurons of the cerebellum, sending crucial information on coordination of complex movements to deep cerebellar nuclei and from there onwards to the cerebral cortex and other higher centers. Loss of excitability of these neurons is sufficient to cause profound ataxia.

The Purkinje neurons are

unique because they are GABAergic inhibitory neurons that serve as projection neurons, in contrast to virtually all other projection neurons, which are excitatory. Dr. Catterall's team believes that the dramatic loss of sodium current in both the hippocampal inhibitory GABAergic interneurons and the cerebellar inhibitory Purkinje neurons means that many classes of GABAergic neurons throughout the brain may have reduced sodium currents and reduced excitability, and that impaired excitability of these other inhibitory neurons may be responsible for other aspects of the disease like spasticity and cognitive impairment. They are beginning to design experiments to test these ideas.

Finally, Dr. Catterall is aware of the abstract, *Dravet Syndrome: Expanding the Clinical Spectrum*, which discusses co-morbid conditions found in Dravet syndrome and was presented at the 2006 annual meeting of the American Epilepsy Society in San Diego, California by Joan Skluzacek, president and executive director of the IDEA League and Dr. Beverly Wical, pediatric neurologist at Gillette Children's Specialty Healthcare and member of the IDEA League professional advisory board. He had not realized, from previous clinical literature, how many different

problems are observed in patients with Dravet syndrome. His lab is now looking for comparable issues in Dravet syndrome mouse models, and then using the mouse model to try to uncover the reason for the disorder. There is hope that this research will bring us closer to understanding the physiochemical aspects of Dravet syndrome and will allow for designing medicines and exploring other treatment options consistent with associated neurochemical imbalances.

References:

Yu FH, Masimo M, Westenbroek RE et al. Reduced sodium current in GABAergic interneurons in a Mouse model of Severe Myoclonic Epilepsy of Infancy. *Nature Neuroscience* 9(9); Sept 2006:1142-49

Personal correspondence with Dr. Bill Catterall regarding pending publication

In Appreciation

The IDEA League would like to recognize the Walker Family—Chris, Candace, Colin, Carson and Cailean—of Grayslake, Illinois for their valuable fundraising efforts. The Walker family recently sold pie certificates and have donated the proceeds from the sales, totaling about \$1200.00, to the IDEA League. The funds will be use to help further the purposes of the League, which are: to promote awareness and research about Dravet syndrome and related genetic, febrile, sodium channel epilepsies and to provide resources and support to improve the quality of life for affected individuals and families. Thank you Walker family for your graciousness and generosity!



Fundraising Forum

By Mary Anne Meskis

The Print Materials Development Team is starting an exciting new fundraiser, in which we hope everyone will participate. We are compiling an IDEA League cookbook that will contain favorite recipes from our member families and pictures of our beautiful children with Dravet syndrome as well .

If you have wondered how you can become more involved with fundraising for the Idea League, here is a great way to start. Each family is asked to contribute one or two of their favorite recipes, a photo (or digital file in jpeg format) as well as a short caption to accompany the photograph. There are several recipe categories, including: appetizers, snacks & beverages, soups & salads,

bread & rolls, vegetables & side dishes, main dishes, desserts, cookies & confections, and miscellaneous. Since the book will contain recipes from around the world, a helpful conversion chart will be included. Don't miss out on the chance to help with a very fun and simple project with us. The more recipes and photos we have, the better the cookbook will be!

All funds raised by sales of the cookbook will help to offset the costs for our upcoming 2008 family and professional conference. This is such a worthwhile endeavor as anyone who attended our first conference can tell you. It made an impact on everyone in attendance, especially the families. Please consider

ordering extra copies to sell as a local fundraiser for the IDEA League or as a gift for family and friends. Your participation will make all the difference.

The cost for the cookbooks will be \$10 USD each + shipping. Pre-orders are encouraged and international shipping is also available. If you have a great recipe you would like to share, please email Michelle Townsend, team leader of the Print Materials Development Team, at shelltown@comcast.net Don't delay! All recipes and photos will need to be received by August 20, 2007.



*The more recipes
and photos we can
include in the
cookbook, the better
it will be!*

Tiger Team Update

By Paula Lyles

I can't tell you how much blood, sweat, and tears would have been spared had there simply been a brochure or poster on Dravet syndrome in our neurologist's office or hospital when my daughter had her first seizure. I might not have given much thought to this syndrome at that time, but surely by the age of two I would have been able to obtain an accurate diagnosis if the information had been readily available.

The Print Materials Development Team is working to do just that. Their goal is to help educate parents of children diagnosed with idiopathic epilepsy about Dravet syndrome, in case it is applicable to their child. They are also working to raise

awareness of this syndrome within the medical community and the general public.

In December, the team published an educational pamphlet for physicians, which has been well received. They are currently working on an awareness poster. The poster explains the condition and asks questions that might help lead to a proper diagnosis of Dravet syndrome. Contact information for the Idea League is provided as well. The goal is to soon have these posters hung in hospitals, clinics, therapy centers, schools, etc.

Other ideas being considered for publication include a parent handbook, a children's book, and a "chicken soup"

type book authored by parents of children with Dravet syndrome. Their latest project, an IDEA League cookbook, is profiled in this issue's *Fundraising Forum*.

This team is headed by Michelle Townsend and members include Karen Glenn, John McMahan, Dina Nelson, Mónica Ramis, Joan Skluzacek, and Mark Zimmerman. The Team welcomes your ideas. Please email suggestions to shelltown@comcast.net

Thanks to this Tiger Team for getting the word out about Dravet syndrome. By doing so, they are helping to make the journey easier for those who have only begun walking down this difficult path.



*The Print Materials
Development Team is
working to educate
parents of children
diagnosed with
idiopathic epilepsy about
Dravet syndrome...*



Angela and Mark Black



Children enjoying the train ride.

Benefit Festival Held in Texas, USA

By Karen Glenn

On April 28, 2007 Angela and Mark Black and family, of San Marcos Texas, hosted an outdoor festival and concert to benefit the IDEA League. The family event, titled 'Let the Children Play', included a variety of activities—such as face painting, train rides and games—as well as a raffle and children's art contest.

With nearby Austin known as the "live music capital of the world", the Black's were able to make use of the availability and generosity of some great live entertainment. Well-known satellite radio performers Staci Gray and Laura Freeman headlined for the children's music, followed later in the day by several talented local bands which performed everything from blues to classic rock.

The majority of the money

raised at the event came from the sale of food and raffle tickets. Appropriate to central Texas, food served included barbeque brisket and sausages in several forms. Hamburgers and hot dogs were also available, as well as snow cones and cotton candy for the kids. Items donated for the raffle included a bicycle with helmet, certificates to local restaurants, karate lessons, a gift basket from Starbucks, and many more. The event was well-attended and raised \$5,000.00 for the IDEA League. In addition, much was done to increase awareness of Dravet syndrome within the local community.

Big thanks go out to all of the businesses and people who donated goods, services and time, and especially to Angela, Mark and the whole Black

family for their many hours of service to make this event possible.

Says Angela, "The Idea League has been such a help to our family as we struggle to help Sarah battle Dravet syndrome. The support we have found through the message board and meeting other families who are facing the same challenges we face has given our family strength and inspiration. We hosted the 'Let the Children Play' Festival and Concert Benefit as a way to give something back to the IDEA League. We hope to make it a yearly event."

Upcoming Events

The IDEA League and its members have several events on the horizon. Join us if you are able!

JULY 2007

- 6-7 Canadian Regional Gathering, organized by Juanita Mason & Marvel McAmmond Calgary, AB Canada
- 14 Townsend Family Benefit, "The Dravet Children's Walk at the Potter Park Zoo" Lansing, MI USA

AUGUST 2007

- 16-19 Family Gathering at Disneyland Resort Paris Paris, France

SEPTEMBER 2007

- TBA Skluzacek Family Benefit, "ValleyStock: A Family Music Festival and Benefit for the IDEA League" Afton, MN USA

FALL 2007

- TBA Midwest Family Gathering Chicago, IL USA

NOVEMBER 2007

- 10 Welborn Family Benefit, "Boogie for Babies 2007" and Parents' Retreat weekend Winston-Salem, NC

AUGUST 2008

- TBA 2nd Biannual IDEA League Family and Professional Conference Location TBA



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