

May conference will mix families with researchers

By Patricia Wood

Topics ranging from the latest research in NBIA to how to talk to children about the disease will be covered at the Third International NBIA Disorders Association Family Conference. It will be held May 20 to 22 at the Gaithersburg Marriott in Gaithersburg, Md., about 30 miles from the heart of Washington D.C.

All NBIA families and individuals should have received their conference registrations forms in February. Registrations are due by April 22. All information and forms are also available at www.NBIAdisorders.org. The conference is open to all NBIA families, friends, members of the medical community and people interested in NBIA.

Family conference registration forms are due by April 22. They are available at our Web site.

In addition to a chock-full agenda of stimulating topics, individual family appointments with Dr. Susan Hayflick, a leading NBIA researcher, may also be available. Priority will be given to new NBIA families. Please contact Allison Gregory at gregorya@ohsu.edu if you are interested to set up an appointment before the conference.

The Second Scientific Workshop on NBIA, which is open to the public, will be held May 19 and 20 at the same hotel. It will bring together scientists from around the world to discuss the latest NBIA research and set directions for future work.

Family conference participants and researchers will be together for a two-hour session Friday afternoon at which time the scientists will update us on their research and take questions.

If you are interested in attending the workshop, an agenda and registration form are also available at our Web site. Please contact me if you have any questions regarding this workshop.

Meeting other NBIA families in person and sharing information and support is a moving, memorable experience, one that families typically say they value most. I encourage all NBIA families to consider joining us if at all possible. Also, having the scientific workshop on site is a big bonus you won't want to miss.

Second annual Scotch Doubles Crazy Bowl raises \$6,000 for NBIA research fund

By Donna Helton



Lauren Williams from Mascoutah, Ill., Wendy Pfeil and Ashley Middendorf from Smithton, Ill. at benefit.

What's a fun, easy way to raise thousands of dollars for NBIA and honor a loved one at the same time? Put on a night of bowling, coupled with a silent auction featuring donated gifts. It's been a winning combination for our family.

For the second year, we've hosted a successful fundraiser in honor of our daughter, Ashley Middendorf of Smithton, Ill. This time, we raised \$6,000 for the NBIA research fund and are planning to make the Scotch Doubles Crazy Bowl an annual event.

We had 72 couples bowling on Nov. 13 and bidding on more than

(see Crazy Bowl on pg. 5)

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What is NBIA?

Neurodegeneration with Brain Iron Accumulation (NBIA) is a rare, inherited, neurological disorder.

The common feature among all individuals with NBIA is iron accumulation in the brain, along with the progressive movement disorder. Patients can plateau for long periods of time and then rapidly deteriorate. The most common symptom is involuntary muscle cramping, called dystonia.

Symptoms vary greatly from one person to the next, partly because the gene affecting them can differ. Different mutations within a gene also can cause a more or less severe form of the disease.

The movement disorders can result in clumsiness, difficulty controlling the body and speech problems. Also common is a degeneration of the retina, which causes night blindness and a loss of peripheral vision.

Some individuals eventually lose the ability to walk, talk or chew food and become totally dependent on others for all their needs.

PKAN knock-out mice created and studied at UCSF

By Allison Gregory



Allison Gregory

The NBIA research teams at UCSF and OHSU recently published an article in the journal *Human Molecular Genetics* describing the creation and analysis of a PKAN knock-out mouse. Knock-out mice are animals that have had a certain gene inactivated, or "knocked out." In this case, the *Pank2* (the mouse gene is referred to in lower case letters, while the human *PANK2* gene is written in all capitals) gene was knocked out, which resulted in a mouse version of classic PKAN.

Knock-out mice can be extremely helpful to researchers by giving clues about the underlying causes of diseases. They also provide an initial way to test possible treatments. Since mice reproduce relatively rapidly (a female mouse is pregnant for only about 20 days before giving birth to a litter of pups), it is possible to design different crosses of mice and collect several generations over a short period of time.

(See *Mice* on pg. 3)

Mice

(continued from pg. 2)

How to make a knock-out mouse

Several advances in technology have made what was previously a stupendous feat a common research tool. The first step is to knock out the gene in a group of mouse embryonic stem cells. Only one of the two copies of the *Pank2* gene is knocked out at this point, leaving the second working copy.

Once the gene has been knocked out, the stem cells are injected into very young mouse embryos created by in vitro fertilization techniques. At this early stage, some of the new cells are incorporated into all the different organs of the developing mice, including the cells that will become sperm and eggs. These embryos are then transferred back into surrogate mouse mothers. About 16 days later, a litter of pups is born. The pups have a mix of normal cells and knock-out cells.

Some pups will have the knock-out gene incorporated in their sperm and egg cells. They are mated and pass on this trait to some of their pups. The pups have the new change in every cell of their bodies and are PKAN carriers. Then, carrier mice are mated to create the true knock-out mouse, which has mutations in both copies of its *Pank2* gene. After three generations of mice and much hard work, several male and female knock-out mice are available to study.

Studies of the PKAN knock-out mice

Several aspects of the mouse's development, health, and physical skills were studied. They were always compared to healthy carrier mice (one working copy of *Pank2*) and healthy normal mice with two working copies of the *Pank2* gene.

The mice were monitored for feeding difficulties and poor growth because these are problems seen in people with PKAN. The knock-out mice were smaller in size and body weight — about 80% the size of the control mice. However, they ate the same amount as the normal mice and did not appear to have trouble with chewing or swallowing. This suggests that there are probably differences in their metabolism that make them smaller.

Fertility was studied in male and female *Pank2* mice. *Pank2* mice cannot mate with each other. The females were found to be fertile when mated to normal mice, but they produced much smaller litters. The males were found to be infertile. Although they produced the precursors to mature sperm cells, their development stopped prematurely and no fully developed sperm were made.

Like people with PKAN, the mice had retinal disease. This was



The mouse with PKAN is the smaller, darker one in the foreground of the picture, compared to the mouse without PKAN behind it. Researchers use a color coat gene to make the PKAN mouse darker so they can easily tell them apart.

shown by electroretinogram studies and by looking by histology at retinal tissue in the laboratory. As in humans, the damage to the photoreceptor cells of the retina worsened over time.

The neurological assessment of the mice was of special interest since PKAN is primarily a neurological disorder. The mice were followed for over a year, which is roughly equal to 34 human years (lab mice usually live about two years). Surprisingly, no evidence of iron accumulation was seen in the basal ganglia and the mice did not have any noticeable neurological impairments. Their brains were evaluated both by magnetic resonance imaging (MRI) and by studying tissue samples from deceased mice. They were given several tests weekly to measure their strength, balance, and muscle coordination.

Discussion of the research findings

The researchers successfully created a mouse that lacks pantothenate kinase 2, the enzyme that is deficient in PKAN. In studying the mice, they found growth problems, retinal degeneration, and absent sperm in the males.

Most surprising was the finding of infertility in the male mice. This has not been described in human males with PKAN, probably because many of the affected individuals with classic PKAN have a shortened lifespan or are very ill. A question for future research is how the *Pank2* protein is involved in the development of mature sperm cells.

Although the retinal degeneration in the mice provides a model for studying this problem in people with PKAN, the mice did not have a movement disorder or show any abnormal iron accumulation in their brains. The next step is to see whether the researchers can bring out these features in the mice. They are currently experimenting with giving the mice various compounds, including a diet that is low in vitamin B₅, to see how deprivation of the vitamin will affect them.



Alyssa Barbiero
April 18, 1996 - December 6, 2004

Alyssa had a special gift. Though only 8 years old, she not only had the ability to deal with her disorder, she had the strength to comfort everyone around her. She was our rock when her big sister passed away in March. She knew exactly when we needed a hug or a kiss, which she showered generously upon us. This past December, we lost her to NBIA. She was our baby girl.

Alyssa was born in Montreal and grew up in a multi-cultural household. Even so, she was adamant about language in the stubborn way she could sometimes be: she only wanted to learn English. She ignored all the other languages spoken around her.

When she was 2, we moved to upstate New York where she attended Clover Patch Preschool. She went on to Rosendale and Birchwood Elementary schools in Niskayuna. In kindergarten, she made some very special friends, friends she would keep for life.

In 2003, she took part in the Make-a-Wish program and said she wanted a dog. This was the happiest event of her life. She picked a puppy from a litter of five black labradors and chose her pet's name all by herself: Emmy. They were inseparable. Alyssa let everyone know that Emmy was her dog. Today it is this affectionate dog that comforts us. Thank you, Alyssa, for this parting gift.

There are so many other people we also want to thank. First and foremost, we are so grateful to our parents, brothers and sister-in-law for all their love and support. We also thank our neighbors who make us feel like family and the staff, parents and students at Rosendale and Birchwood. They always made Alyssa feel comfortable.

To all of Alyssa's instructional aides and teachers, we know she had

the best, and we thank you. Your determination and dedication made her love going to school.

Thanks to all of Alyssa's bus drivers and aides who made her rides to school fun. And thanks to the Niskayuna School District for taking care of all of her needs.

Special thanks to Pat Sweeney, Deidra McGuire, Laura Lape, Ali Lerner-Doyle, Megan Adams and the Michalisins for taking care of Alyssa and bringing her so much joy. Heartfelt thanks to Holly Lape, who was a very special person to Alyssa and remains the foundation of our family. Holly has stood by us through thick and thin and is our guardian angel.

To Niskayuna residents, our wonderful community, which continues to help us through this very difficult time, we appreciate you so much. To all of our friends, you know who you are, thank you for helping us.

Last, but not least, thanks to Brian Alyward and Mark Michalisin who brought out Alyssa's true character in their touching eulogies. No words can express our gratitude to you. The smile you would bring to Alyssa's face told us she was a very lucky girl to have known you — and all who touched her during her all-too-brief time with us.

Alyssa's passing has left a large hole in our lives that will never be filled. But she will live forever in our hearts. Thanks, Alyssa, for bringing joy and strength into our lives and teaching us the true meaning of life. We were truly blessed to have you as our daughter. We will never stop missing you!

All our love Mom, Dad and Emmy



Sabrina and Alyssa Barbiero both lost their battle with NBIA in 2004, within a span of 8 months. Sabaly stands for the first three letters of Sabrina and Alyssa put together and was a special word the girls loved.

Their Uncle Anthony created a Web site at www.sabaly.org to raise awareness around the world about NBIA. The hope is to raise enough money to continue and expand research, with the ultimate goal to find a cure so that other kids and families do not have to suffer.

Visit their Web site at www.sabaly.org

Crazy Bowl

(continued from pg. 1)

120 items and gift baskets donated by businesses and individuals in our community. We also held three raffles. The grand prize for one of the raffles was a wheelbarrow filled with booze.

The bowling alley was filled with laughter and excitement throughout the evening and everyone commented on having a wonderful time. We look forward to doing it all again next year.

Please contact info@NBIAdisorders.org if you are interested in having a fundraiser. We have handouts and information on fundraising and will be happy to assist you with your planning.



Silent Auction items on display at Crazy Bowl fundraiser.

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You can honor the memory of a loved one or a friend through a gift to NBIA Disorders Association. The thoughtful people listed below have made a donation on behalf of their friends and loved ones during the last few months.

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MESSAGE FROM THE PRESIDENT

Lots of calls bring sad news but reasons to hope remain



Patty Wood

When my older relatives were alive, phone calls at strange hours always upset me. That was how I found out my grandmother, my mother, a favorite aunt and even a young brother-in-law had all passed away.

These past two years have been hard ones for me and my NBIA family. We've lost eight to the disease — that I know of — and there are others who are critically ill. My heart goes out to all of those families. As I have taken these sad calls during the past two years because someone has lost a son, a daughter or a sister to NBIA, I feel so helpless. I can't help but wonder when the pain will stop.

At times like that, it is easy to feel defeated. It is easy to believe NBIA will always be with us. But we have seen advances in medicine these last few years that we could not have imagined a decade ago. The discovery of a NBIA gene is a huge advance.

There is reason to hope for a better tomorrow. But we have to work for it. We must keep fighting together for the day when there is a cure for this disease. Then these phone calls will be in our past and no longer a terrible reality for NBIA families facing uncertain futures.

NBIA research is our hope. We must do all we can to promote and support research into this disease. The Second Scientific Workshop on NBIA will be held in May. This is an important step. It will bring together scientists from around the world who can share information and ideas. They also will have a chance to meet with families who grapple with this disease on a daily basis and learn from them. Those families will, I hope, include many of you gathering for the Third International Family Conference.

The Genetic Alliance BioBank of which our organization is a founding member, is another important step for our organization in our efforts to increase research into our disease. Our hope is that this will encourage new researchers to enter the field.

Families holding fundraisers in their communities to raise awareness of the disease and funds for research grants are vital also to fund the research grants we hope to continue to award in the years ahead.

We must stay strong as a family — united in our support of each other and united in our work to help find a cure. Let's pledge to never stop until the phones stop ringing.

NBIA Disorders Association is grateful to its supporters for their generosity. We extend our deepest thanks to the contributors listed below who have donated in the past few months.

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- Administration (2%)
- Web site (9%)
- Scientific Workshop/Family Conference (5%)
- Newsletter (20%)
- Research Grants (64%)

Administration	\$ 1,576
Scientific Workshop/Family Conference	3,665
Web site	6,046
Newsletter	14,344
Research Grants	45,033
Total	70,664



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Our Mission:

NBIA Disorders Association is a non-profit organization dedicated to providing emotional support to families affected by NBIA, educating the public about this disease, and monitoring and supporting research and informing others of its progress.

NBIA Disorders Association

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