

SPRING 1999

VOLUME 6, NO. 1

"NEVER**DOUBT**

that a small

group of

thoughtful,

committed

citizens can

change the

world.

Indeed, it's

the only

thing that

ever does."

— Margaret Mead

Member Update

Workshop on Fragile X: Future Research Directions

On December 3rd and 4th, in Washington, DC, the National Institute of Child Health and Human Development (NICHD) and FRAXA cosponsored a workshop on fragile X. It was a rare privilege to sit around a table for two days and watch 28 top geneticists, neuroscientists, psychologists and physicians tackle the key question: what research needs to be done to treat or cure fragile X? We are deeply thankful to all the participants who shared their thoughts and expertise. Judging from the participants' comments we have received, meetings such as this are very worthwhile:



"I'm not a Fragile X researcher, but after the last 36 hours, I'm beginning to wonder why" – William McIlvane, Ph.D. Eunice Kennedy Shriver Center

"After reviewing the literature (on fragile X), at Dr. de la Cruz's request, I'm an instant convert. Fragile X is a window into understanding hyperactivity." – Judith Rapoport, M.D. Chief, Child Psychiatry Branch, National Institute of Mental Health

"The meeting helped focus my energy on the important issues regarding fragile X syndrome. Talking with the other participants, I know they feel the same way . . . Small meetings, limited to 20-25 key investigators, really do stimulate collaborations and push the envelope for new insight and avenues of research." – Stephen Warren, Ph.D. Emory University School of Medicine

FRAGILE X FUTURE RESEARCH DIRECTIONS WORKSHOP PARTICIPANTS:

Duane Alexander, MD, Director, NICHD; Don Bailey, Ph.D., Univ. of North Carolina; Mark Batshaw, MD, George Washington Univ., Joel Bregman, MD, Yale Univ., Marie Bristol-Power, Ph.D., NICHD; W. Ted Brown, MD, Ph.D., NY Inst. for Basic Research; Katie Clapp, M.S., FRAXA; Edwin Cook, MD, Univ. of Chicago; Linda Crnic, Ph.D., Univ. of Colorado; Felix de la Cruz, MD, M.P.H., NICHD; Lisa Freund, Ph.D., NICHD; William Greenough, Ph.D., Univ. of Illinois; Randi Hagerman, MD, Children's Hospital, Denver CO; Herbert Lubs, MD, Univ. of Miami; Edward McCabe, MD, Ph.D., UCLA; William McIlvane, Ph.D., Eunice Kennedy Shriver Center; David Nelson, Ph.D., Baylor College of Medicine; Giovanni Neri, MD, Universita Cattolica; Ralph Nitkin, Ph.D., NICHD; Ben Oostra, Ph.D., Erasmus Univ.; Mary Lou Oster-Granite, Ph.D., Univ. of CA; Judith Rapoport, MD, NIMH; Allan Reiss, MD, Stanford Univ.; Owen Rennert, MD, NICHD; Francois Rousseau, MD, Hospital St. Francois D'Assise; Stephanie Sherman, Ph.D., Emory Univ., Steven Walkley, DVM, Ph.D., Yeshiva Univ.; Stephen Warren, Ph.D., Emory Univ.; Huntington Willard, Ph.D., Case Western Reserve Univ.

Fragile X Workshop continued on page 3

Inside this issue:

- Financial Report: Wrapping up 1998
- FRAXA and NICHD Co-Sponsor Research Conference
- New research projects funded
- Report from Washington
- Chapter News and Events

FRAXA is a nonprofit, tax-exempt private charity run by parents of children with fragile X syndrome. Fragile X syndrome is the most common inherited cause of mental retardation and developmental disabilities, affecting approximately 1 in 2000 males and 1 in 4000 females. FRAXA's goal is to accelerate research aimed at the treatment of fragile X, by direct funding of promising research projects and by raising awareness of this disease.

Report from Washington

by Mary Beth Busby



Mary Beth and David Busby

Editor's Note:

FRAXA's Vice President Mary Beth Busby was featured on the Diane Rehm Show's, "Women at Work" on National Public Radio, October 2nd. In this interview, she spoke about her experiences working with FRAXA on behalf of her sons, Jack and David, Jr., who have fragile X. If you would like a tape of this segment, contact WAMU at (202) 885-1200.

Help!! We need help! But first the good news. The December 3-4 Research Conference, which FRAXA and the National Institute of Child Health and Human Development of the NIH sponsored together in Washington, was a great success (see article, p.1).

As you will remember, this international conference

of the top Fragile X researchers was called for in last year's Reports of the Appropriations Committees of the House and Senate (at FRAXA'S – and your – urging!). FRAXA hosted the dinner. Senator Dale Bumpers (by videotape made earlier) and NICHD head, Dr. Duane Alexander, presented FRAXA'S beautiful engraved crystal hurricane lamp to the head of the Mental Retardation Branch, Dr. Felix de la Cruz (see box, p. 8). In his kind and gentle way, Dr. de la Cruz emphasized the spirit of sharing ideas about the best direction of future research. The Conference Report will be a research road map! The researchers themselves were very optimistic about breakthroughs.



Dr. Duane Alexander, Chief, NICHD

Now for the "Help!!" part. The second annual Mary Higgins Clark Fragile X Gala will be here in Washington on Monday, April 19th at the Four Seasons hotel. Tickets \$350 each; \$260 tax deductible. We want as many parents and supporters as possible to be with us, and with Mary Higgins Clark herself, for this special occasion. We need you! I realize that this is a big ticket item . . . we do expect to get some underwriting, which will make a very large percentage of your dollars go straight to research, and not to the Four Seasons Hotel, which,

by the way, is giving us a wonderful deal on the Gala. National Public Radio talk show host, Diane Rehm, will co-host the dinner with me and will look forward to seeing you as much as I will. So, ya'll come, okay?

Now, the other "Help!" item is something that will really be great fun. We are working on an initiative that can provide major funding for fragile X research. We will take advantage of the sterling presence of those of you who will be here for the Gala to have our first "Lobby Day" the morning after the Gala, on Tuesday, April 20. We'll all meet for breakfast to talk about what we want to talk about with our (I should say "your") members of the House

Dr. Randi Hagerman, Denver Children's Hospital and Dr. Marie Bristol-Power, NICHD

and Senate. We'll distribute packets and some general guidelines, and then we'll fan out over The Hill. Keep in mind that your Senator or House Member will likely send you to meet with his or her medical staff person; but that's okay. That's the way it works. These



are the people who advise the Members on what's important to their constituents (you).

To set up your appointment, simply write to your Congressman or Senator, say you'll be in town that morning, and would like to drop by to talk about Fragile X. He or she will likely say, "What?" But that's okay. You'll tell them what.

If you need ideas as to how exactly to do this, contact the Lobby Day coordinator, David Busby, at 202-452-6920, or e-mail him at



Owen Rennert, NICHD; Lisa Freund, Ph.D., NICHD; Joel Bregman, Ph.D., Yale; and Don Bailey, Ph.D., UNC, Chapel Hill

busby.david@dorseylaw.com. Also please call David right away if you are personally acquainted with any member of Congress. DON'T wait until you get here for the Gala to ask for your Lobby Day appointments. Do that as far in advance as possible. Like now. (Addresses: Senate Office Building, Washington, DC 20510; House Office Building, Washington, DC 20515.) You can always just drop in to leave some information or say hi; but if you want to "see" somebody, you must make an appointment. Unless you're very lucky and/or very important.

Lest this idea of a Lobby Day seem a bit daunting, let me just remind you that these people are in office because you say they should be there, and they know that probably better than you do. If you're not happy, they're outta here next time around. Remember, our children can't speak for themselves, so we must speak for them. So, ya'll come to the Gala and Lobby Day, too. Do come and enjoy Washington's most colorful month of the year. I remember the little saying to the effect that the beautiful flowers of tomorrow are really only the seeds of today. I truly think you'll find it exhilarating to plant these seeds, which will, I'm convinced, grow into awareness and research breakthroughs which will benefit our children.

Christmas letter though I am sure a Christmas letter would be easier to write. This is instead a letter from the heart which Enzo and I have been wanting to write for many years and have not had the courage to do so. It has always been our nature to do things by ourselves and not ask others for help. As you may or may not know, our son Michael has an inherited disease called Fragile X . . ." The impact of Kitty and Enzo's letter is still growing: it has taught many people about fragile X, it has raised over \$25,000 for FRAXA and still counting! Thank you, Kitty and Enzo.

WISCONSIN

Rachel Dunham writes from Washburn, (pop.2,000): Mark, the senior class president at Washburn High brought FRAXA information to the school. They are excited about their senior class fundraising drive for FRAXA! They are sending out notes to the entire school population — every parent will want to help their kids. They are dividing the class into three teams. Each team has a penny collecting jug, and they get prizes for the fullest jugs. It has to be pennies — if you have silver in your jug, you LOSE



Martha Matthews with her penny bank

points, but that means trying to sneak it into your opponents' jugs! Let's hope for a lot of sneaky high school seniors!!! The Pennies for FRAXA campaign has spread to Texas (thank you, Suzanne Silva) and Florida (thank you, Martha Matthews)!

TEXAS

Roger Hoh represented FRAXA at the TEXGENE Conference in San Antonio and the Alliance for Genetic Support Groups Confer-



Suzannah Dickman

ence in Washington, DC. Roger reports that the TEXGENE Conference was great: "There were over 100 people there. Most of the newsletters, AAP article, and brochures were picked up. At the poster session, the best poster was my committee's, comprised of photos of people with genetic conditions. FRAXA really stood out as being one of the more successful groups." Susannah Dickman of El Paso helped Roger Hoh staff a FRAXA booth at the Alliance of Genetic Support Groups Conference in Washington, DC.

MISSOURI

The Fragile X Resource Center of Missouri has supported FRAXA generously over the past few years and has pledged to do so again in 1999. We thank all the members of this dynamic and determined chapter!

OHIO

At the request of Alice Bagdasarian, an endowment fund was established in the memory of her husband Alex A. Bagdasarian who passed away on August 20. Memorial donations made in lieu of flowers totaling \$5,600 were collected and sent to FRAXA to support Fragile X Research. The Bagdasarians, of Cleveland, Ohio, have two grandchildren, Julie (7) and Alex (5) who are affected by Fragile X Syndrome. The family plans to continue donating to this fund on an annual basis. FRAXA research grants. FRAXA would like to give special thanks to Alice Bagdasarian and the Bagdasarian family for establishing this endowment fund.

FRAGILE X LISTSERV

This is a virtual support and information exchange group for all interested parties, including parents, other family members, educators, and medical professionals. We are grateful to Emory University for sponsoring this listserv. Directions for joining are at Fraxa's web site: www.fraxa.org.

MATERIALS AVAILABLE:

FROM NICHD:

National Institute of Child Health and Human Development has published a free brochure on fragile X syndrome. Copies of this brochure can be requested from the NICHD Clearinghouse, Phone: (800) 370-2943 Fax: (301) 984-1473 Website: <http://www.nih.gov/nichd>

FROM FRAXA:

Fragile X Information Cards

These are business-size cards that fit in a wallet. \$10 per 150.

NEW! Fragile X Articles

The Advocate 1995 - 1997 published by Avanta Media Corp. 173 pages of top notch articles written by dozens of professionals and family members on all aspects of fragile X. \$25

A Medication Guide for Fragile X Syndrome

by Michael R. Tranfaglia MD, Psychiatrist, Medical Director of FRAXA. \$25

Fragile X - A to Z

Hints from and for families extracted from the Fragile X Listserv, an online support group open to all (visit www.fraxa.org) \$10

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AWARDS RENEWED JANUARY 1999

5. Restoration of Natural FMR1 Expression in FMR1 Deficient Mice by P1 Artificial Chromosome (PAC) Transgenesis

ROBERT BAUCHWITZ MD, PH.D. Principal Investigator Columbia Univ., NY, Project Grant funded Jan 1999 (\$30,000)

6. Isolating and Characterizing the mRNAs that Bind FMRP

ROBERT DENMAN PH.D. Inst. for Basic Research, Staten Island, NY. Postdoctoral Fellowship (\$30,000) Renewed January 1999 (\$30,000)

7. Studies of the Function of the Fragile X Mental Retardation Protein

WILLIAM GREENOUGH PH.D.

Univ. of Illinois, Urbana-Champaign Interim grant funded December 1995 (\$14,000); summer internship funded June 1997 (\$5000) Postdoctoral Fellowship funded January 1996 for 1 year (\$25,000); Unrestricted Grant funded January 1997 (\$50,000). Project Grant funded January 1998 (\$150,000). Renewed January 1999 (\$100,000)

8. Export of the Fragile X Gene Product

ALAN TARTAKOFF PHD Case Western Reserve Univ., Cleveland, OH. Postdoctoral Fellowship (\$30,000) Renewed January 1999, (\$30,000)

New FRAXA Awards Funded January 1999

Thanks to the generous support of our contributors in 1998, FRAXA was able to fund four new research projects and renew four ongoing projects. FRAXA is now sponsoring research on fragile X at 15 universities around the world. We support research aimed at treatment for fragile X on several fronts: gene therapy, protein replacement, gene repair, and psychopharmacology, to name a few. We will continue to support promising research until an effective treatment or cure for fragile X has been found.

1. The Role of the Fragile X Mental Retardation Protein in the Development and Functional Maturation of Spine Synapses in Vitro

MENAHEM SEGAL, PH.D.

Weizmann Institute, Israel (Project Grant, \$40,000)

KATARINA BRAUN, PH.D.

Leibniz University, Germany (Project Grant, \$40,000)

WILLIAM GREENOUGH, PH.D.

University of Illinois (co-investigator; already funded by FRAXA)



Menahem Segal, Ph.D.

A stunning observation made decades ago is that major deficits in the ability to acquire and store information, as is the case of mental retardation, is associated with minimal, if any, change in the structure of the brain. While scientists are still puzzled by the lack of apparent difference between the brain of a



Katarina Braun, Ph.D. and research team

research

genius and that of a mentally retarded person, exciting information which can explain how an organism becomes mentally retarded begins to emerge. It focuses on the dendritic spine, that part of a nerve cell which is the locus of synaptic interaction, neuronal plasticity and long term memory. The recent advent in molecular cloning helped in isolating the protein FMRP, which is absent in Fragile X mentally retarded children, and morphological studies have linked this protein to the dendritic spine. Also, the morphology (shape) of synaptic structures is abnormal in Fragile X syndrome. Having access to new and advanced technologies, we have now reached a turning point where, for the first time, it is possible to address these issues in our established models for synaptic plasticity.

The objective of the current proposal is to better understand the role of FMRP in synaptic structure and function in a controlled, *in vitro* test system involving the tissue-cultured neuron. We propose the hypothesis that mental retardation, typical of patients with the fragile X syndrome, may be manifested by abnormal and malfunctioning synaptic connections. We also propose that expression of FMRP at the synapse could be involved in the synapse maturation process. A continuing role of FMRP expression in adult synaptic plasticity may indicate that synaptic FMRP synthesis is a critical factor in synapse stabilization and elimination, both in developmental brain organization and in adult learning and memory. We will analyze FMRP-mediated functional maturation of spine synapses in two brain regions, the *hippocampus* and the *anterior cingulate cortex*. Both regions are known to mature during late postnatal stages and therefore are vulnerable to disruption of normal synaptic selection processes. Both brain regions are part of the limbic system, which mediates emotional responses as well as learning and memory formation, functions that are severely impaired in the fragile X syndrome. We will study the expression of FMRP in developing cultured hippocampal and cortical neurons and follow the responses of these neurons to experimentally-induced changes in synaptic activity. We will modify the expression of FMRP and study the changes in synaptic properties and integration of the affected neurons. The identification and characterization of the role of FMRP in normal and pathological synaptic plasticity during brain maturation is a prerequisite for future design of clinical preventive or therapeutic strategies for the treatment of mental retardation associated with the fragile X syndrome.

in vitro/in vivo *"in vitro"* refers to experiments on tissues in lab dishes, as opposed to *"in vivo"* which means experiments done in live animals or humans.

synapse A synapse is a junction between one nerve (brain) cell and another. The brain works by passing signals from one cell to the next, via synapses.

plasticity The ability to change, or mold, the shape of something. Synaptic plasticity refers to the fact that the shape and size of a synapse can change as a result of learning, making it more (or less) likely to pass a signal to the next cell. This phenomenon is thought to be critical for learning and memory.

update:

2. Identification of Specific RNA Targets of FMRP

ROBERT DARNELL, MD, PH.D. Principal Investigator

JENNIFER DARNELL, PH.D. Postdoctoral Fellow



Robert Darnell, MD, Ph.D.

Rockefeller University (\$35,000)

A single amino acid change in the protein FMRP, the lack of which causes the fragile X syndrome, can result in especially severe fragile X symptoms. This amino acid is in a domain of the protein responsible for binding to RNA, and it has been shown that this mutation decreases FMRP's ability to bind to RNA. It is important to identify the RNA species within the cell to which

FMRP binds, because it appears likely that the loss of binding to such RNAs causes fragile X syndrome. To this end, we have developed a method of selecting RNA species from a random pool of RNAs which bind to FMRP. Sequencing the RNAs which bind most strongly to FMRP has allowed us to define a consensus RNA sequence which confers high affinity interaction with FMRP on an RNA. Comparing this sequence to the sequences of cellular RNAs will allow us to identify and test real RNA species for interaction with FMRP. In addition, we have developed methods for crosslinking proteins with RNA in the cell and then purifying and sequencing these molecules. This approach, applied to FMRP, should allow us to identify its cellular targets. Combined, these experiments are likely to yield new insight into the essential function of FMRP as an RNA-binding protein in the brain and suggest potential points of therapeutic intervention.

3. Reactivation of the FMR1 Gene in Fragile X Patients Cells in Culture

GIOVANNI NERI, PH.D.

Catholic University, Rome, Italy (Project grant, \$30,000)

Our project is based on the fact that in 99% of the fragile X syndrome patients, the coding region of the FMR1 gene is intact and its loss of function is due to the CGG expansion and methylation of the regulatory region at one of its extremities. One can say, in a simplified manner, that the gene is switched off and that we are trying to find a way to switch it back on. Since methylation is a key factor in the silencing of the gene, our first approach was to treat in vitro cell lines from fragile X patients with the demethylating drug 5-azadeoxycytidine. This treatment reactivated FMR1 gene transcription and restored production of its protein product FMRP (Chiurazzi et al., Hum Mol Genet 7, 109-113, 1998). Now we plan on

extending our original observations to a larger number of cell lines and at the same time on trying other compounds that have the potential to reactivate the FMR1 gene. One promising compound is butyrate, which acts on DNA-associated proteins called histones. Histones play an important role in the regulation of gene activity and

in the past we were able to show that treating fragile X lymphocytes (blood cells) with butyrate resulted in a reduced manifestation of the fragile site FRAXA (Pomponi and Neri, Am J Med Genet 51, 447-450, 1994). Butyrate is a drug of limited toxicity and the results obtained with the in vitro experiments could lead to eventual in vivo trials (in live animals or human patients.) International collaboration with other distinguished groups (Ben A. Oostra, Rotterdam; Steve Warren, Atlanta) will allow the sharing of expertise and will help in developing new ideas and new approaches.



Giovanni Neri, Ph.D. (left) and collaborators

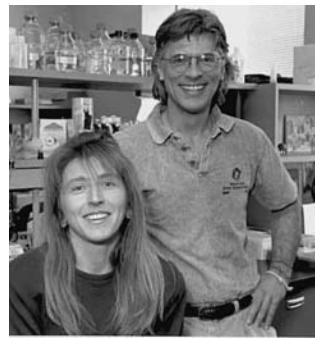
4. FMR1 Gene Regulation

PAUL HAGERMAN, PH.D. Principal Investigator

FLORA TASSONE, PH.D. Postdoctoral Fellow

University of Colorado, Denver (\$30,000)

Fragile X syndrome is usually caused by a large expansion of a CGG trinucleotide repeat in the FMR1 gene. Full mutations (greater than 200 repeats) are generally associated with methylation of CG-rich "islands" upstream of the gene. This expansion and subsequent methylation reduces or "silences" (turns off) transcription of the FMR1 gene so that it produces too little or none of its normal protein product (FMRP).



Flora Tassone, Ph.D. and
Paul Hagerman, Ph.D.

Studies with other human genes have provided evidence that methylation itself may not cause silencing of these genes. Rather, the methyl groups appear to act as signals for the modification of associated chromosomal proteins (histones) to a form that prevents transcription of these genes. Genes that are transcriptionally active (i.e., "turned on") normally possess histones with acetyl groups attached. However, when a gene becomes

methylated, enzymes called "histone deacetylases" are recruited to remove the acetyl groups from the histones near the gene. For a number of human genes, it has been shown that transcriptional activity can be at least partially restored by blocking the deacetylase with one or more drugs (histone deacetylase inhibitors). These inhibitors have not been examined in detail for the FMR1 gene. In one phase of our investigations, a number of histone deacetylase inhibitors will be examined in cell culture for their ability to restore transcriptional activity of the FMR1 gene (turn the gene on). In a second phase of our research, quantitative methods for measuring FMR1 RNA levels will be used to better define the level of transcriptional activity.

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FRAXA Chapter News

CALENDAR OF EVENTS Fundraisers for FRAXA

APRIL 19, WASHINGTON, DC THE FOUR SEASONS HOTEL

2nd Annual Mary Higgins Clark Gala Contact: Mary Beth Busby at (202) 462-2323, email MBBusby@aol.com

MAY 6, PHILADELPHIA, PA THE RITZ-CARLTON

2nd Annual Philadelphia Gala contact: Cristy Hollin at (610) 239-9075

MAY 14, PORTLAND, OR THE BENSON HOTEL

Dinner hosted by Mary Higgins Clark, with entertainment and an auction. Contact: Karen Ripplinger at (503)973-3006, email GKRIPP@aol.com

MAY 23, CHICAGO, IL

2nd Annual Family Fun Day contact: Jody Goldsmith at (847) 831-3669, email JAGAMP@aol.com

JUNE 6, CAMBRIDGE, MA

3rd Annual 3-on-3 Basketball Tournament. contact: Pamela Vershbow at (617) 924-7560

JULY 19, 1999, LYNDHURST, OH

3rd Annual Fragile X Golf Benefit, at the Acacia Country Club, by the Fragile X Alliance of N.E. Ohio. Silent and live auctions will be held. Contact: Leslie Bagdasarian at (440) 519-1517, email lbagdas@cyberdrive.net

OCTOBER 17, WOBURN, MA

Craft Luncheon and Auction contact: Pamela Vershbow at (617) 924-7560

FEATURED CHAPTERS NEWS

Please send in your news to Wendy Dillworth, Chapter Coordinator for FRAXA. Call Wendy at (616) 629-5890, email: compose12@aol.com, to explore ideas for growing your

chapter or starting a new one. Or, call Katie Clapp at FRAXA Headquarters (978) 462-1866, email: kclapp@fraxa.org. A complete listing of FRAXA's 27 chapters is available from FRAXA or on the web at www.fraxa.org/chapters.html. This issue, we are featuring the following chapters:

MASSACHUSETTS

Please make certain you've updated your records with our new address: 45 Pleasant Street Newburyport, MA 01950 Phone: (978)462-1866 Fax: (978) 463-9985

Monthly support group meetings for families meet every month. Please contact Sandra Morse at Family TIES, N.E. Regional Health Office, Tewksbury Hospital, Tewksbury, MA 01876. Phone: (978) 851-7261, email: OldeMissy@aol.com

ILLINOIS

The Wisniewski/Nichols family has helped FRAXA through several fundraising activities. Laura Nichols writes: "We held three Jewel-Osco Shop-N-Share benefits . . . days on which the food store Jewel-Osco will donate 5% of the total spent by each participant. My family and I passed out more than 500 participation slips for each benefit." In addition, Laura's company, Arthur Anderson, and Casey Wisniewski's company, Environmental Systems Design, each chose to support FRAXA at their 1998 Christmas party.

PHILADELPHIA

Thanks to Cristy Hollin, the city of Philadelphia officially celebrated November 19th, 1998 as Fragile X Day. This was a terrific way to bring awareness to our cause. On November 19, 1999, we hope cities across America will celebrate



Philadelphia celebrates November 19th, 1998 as Fragile X Day.

Fragile X Day. Please contact Cristy at (610) 239-9075 to learn how you can get the wheels turning in your city.

NEW YORK

Deborah and Frederick Jaccarino

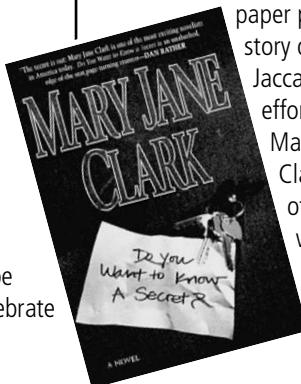


ran the entire 26.2-mile New York Marathon, raising pledges for FRAXA. Deb writes "we got involved because of my husband's college roommate David Clark. His son Davey has fragile X. We attended your fundraiser in NY last April and were quite impressed with your work."

Friends and family made pledges

and the local town paper printed a story on the Jaccarinos' efforts.

Mary Jane Clark (mother of David, who has fragile X, member



of the FRAXA Board of Directors, published her first novel in November. *Do You Want to Know a Secret?* is a terrific thriller featuring a young man with fragile X who holds the key to the mystery. The book has a growing international following: 30,000 copies sold in Germany in two months and Japan has recently purchased translation rights. Many thousands of people will now know about Fragile X.

VIRGINIA

Brian and Carol Colligan, J.D. Fowler, Kathy May, and several other volunteers manned the concession stand at the Fairfax County Police Union's motorcycle rodeo. At the end of the day, FRAXA had realized over \$2,100. Thank you to everyone who made this such a successful event . . . next year, we hope to have photos of the officers on their Harleys!

NEBRASKA

NEW CHAPTER!

Megan Massey has kicked off a new FRAXA chapter in Nebraska. You can reach her at: 90473 28th Ave. Scottsbluff, NE 69361. (308) 635-7109

WASHINGTON, DC

Kitty and Enzo de Chiara wrote a wonderful letter to their friends, relatives and colleagues. Their letter begins: "No, this is not a belated

A conference report is being issued jointly by NICHD and FRAXA, to pinpoint future research directions and funding priorities. In particular, the following excerpts indicate just how critical it is that we all work together and share research.

Workshop on Fragile X: Future Research Directions

December 3-4, 1998, Sponsored by National Institute of Child Health & Human Development and FRAXA Research Foundation

GENERAL RECOMMENDATIONS

Network Approach:

The investigative approach to Fragile X syndrome is, and must continue to be, nonlinear. As was pointed out at several times during the Conference, the fundamental biology of Fragile X syndrome involves parallel and interacting pathways, in other words, a network. Therefore, understanding pathogenesis, as well as effective approaches to treatment will require an appreciation of the network model.

Parallel Strategies:

Simple approaches to intervention will be much less effective than multiple parallel strategies. For example, approaches to treatment should necessarily include simultaneous study and intervention involving the same patients with behavioral as well as drug approaches.

Human Imperative Demands Timely Action:

The patients and their families represent the human imperative for effective interventions to improve the outcome of individuals with Fragile X syndrome. In addition, the FRAXA Research Foundation and the families have been important in obtaining the attention of the legislature and it is critical that the Foundation and the families continue to be involved intimately as partners in the strategic approach to solving the fundamental and clinical problems related to Fragile X syndrome."

Multi-center collaborations:

In addition, the need for long-term funding to create multi-center collaborations was emphasized by a number of speakers at the conference:

By eight years of age, the majority of children with Fragile X syndrome are exposed to clinical therapies for which there are generally no data on safety or efficacy. Frequently children may have paradoxical effects from their medications. The relatively small groups of patients who are seen by most individual clinicians are insufficient for carrying out well-controlled clinical trials. Therefore, there is a definite need for multi-center, collaborative studies that will not only help to evaluate efficacy of drug therapies and potential side effects of these medications, but will also permit a better correlation between biological variables and clinical phenotype."

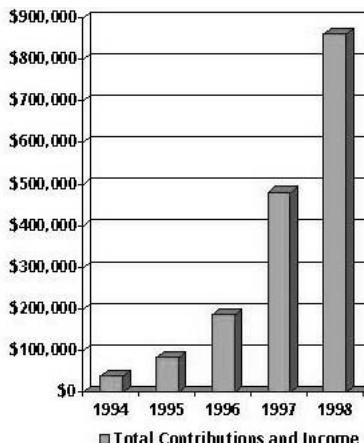
FRAXA is now working with the NICHD and Congress to implement these suggestions. Following the workshop, representatives from FRAXA and NICHD met to discuss setting up a special Request for Applications (RFA) for fragile X research. An RFA is a targeted program that sets aside a block of money for fragile X research. FRAXA offered to contribute 20% of the cost of this program, and NICHD officials agreed to establish an RFA as soon as funds for this purpose can be identified.

FRAXA FINANCE REPORT: WRAPPING UP 1998

THERE IS BAD NEWS

AND GOOD NEWS about our fifth year of funding fragile X research: the bad news is that, for the first year ever, contributions to FRAXA did not double. The good news is: they almost did!! To date, FRAXA has funded 22 research grants, totalling over \$1,189,000. In addition, thousands of people have learned about fragile X through FRAXA's free web site and listserv and through our publication. We

thank everyone who has helped make 1998 an extraordinary year. Please forgive any omissions, which are entirely the fault of the editor.



TRULY EXTRAORDINARY DONORS:

Anonymous
Mary Higgins Clark
Fragile X Alliance of Northeast Ohio
FRAXA Philadelphia Chapter
The Meadows Foundation

MAJOR GIFTS (\$5000+)
Anonymous (4)
Ara and Leslie Bagdasarian
David Clark
Carol Higgins Clark
Raymond and Ellen Goldberg Foundation
Mr. and Mrs. Harris Hollin
Marjorie and Lewis Katz
The Howard and Debbie Schiller Foundation
Ruth and Daniel Vershbow

RESEARCH UNDERWRITERS (\$1000+)

Mr. and Mrs. Leonard Abramson
Abramson Family Foundation
Bader Alrumaih
Alter Foundation
Robert and Nancy Ascher
Fred and Doris Behrends
William and Sylvia Bell
Marc and Suzanne Bell
Roger and Barbara Brannon
Anthony Brenner
Arthur and Nancy Broll
Raymond and Joan Burns
Mary Beth and David Busby
Charles Chamberlin
Marie Rizzo and Victor Cioppo
Anne Clapp
Mary Jane Clark
Marilyn Clark
Warren Clark
Amy Hewes and Kevin Clark
Patricia Cloherty
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Wendy and John Dillworth
Patricia and William Doering
Mr. and Mrs. John E. Dunsford
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Fragile X Resource Center of Missouri
David and Cynthia Friedman
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William Gaspero
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FRAXA POSTDOCTORAL FELLOWSHIPS REQUEST FOR GRANT APPLICATIONS

Upcoming Deadlines: May 1, 1999 and November 1, 1999

FRAXA's grant program is designed to encourage research aimed at finding a specific treatment for fragile X syndrome. Awards of up to \$30,000 each per year are offered to support postdoctoral fellows who want to pursue research in fragile X. FRAXA also invites investigator-initiated research applications for innovative pilot studies aimed at developing and characterizing new therapeutic approaches for the treatment and ultimate cure of fragile X syndrome.

FRAXA is particularly interested in preclinical studies of potential pharmacological and genetic treatments for fragile X and studies aimed at understanding the function of the FMR1 gene. Please contact FRAXA for information or visit the Web at <http://www.fraxa.org/>.

Senator Dale Bumpers' Presentation at the NICHD/FRAXA Dinner Honoring Dr. Felix de la Cruz, December 3, 1998

"I am pleased and honored to be here tonight, in spirit, to help honor Dr. Felix de la Cruz for his wonderful, compassionate years of working in the vineyard of child health, in the field of mental retardation. Just think of all the research breakthroughs he has seen, in many of which he has lent a hand.

Needless to say, we public servants are particularly proud to be part of the accomplishments of the NICHD. In our Committee's report to the Senate last year, we applauded the work of The National Institute of Child Health and Human Development and urged the Institute to sponsor a colloquium to bring together the leaders in the field of fragile X research. Well, here you are! We are gratified by this response! We also applaud the work of FRAXA, the joint Sponsor with the NICHD of this colloquium. I wish each of you distinguished scientists gathered here good luck and Godspeed in finding a breakthrough for fragile X. The future worlds of thousands of children will be shaped by your efforts. And now, I would like to join FRAXA in presenting this crystal lantern to Dr. de la Cruz, as a symbol of our appreciation of his work and leadership in child health. The inscription reads:

"FRAXA Research Foundation presents this award to Dr. Felix de la Cruz, a pioneer in the search for the discovery of the causes of, and help for, mental retardation in children. His work will endure as a beacon to inspire the search for a cure for fragile X. December 3, 1998 "



Dr. Felix de la Cruz receives FRAXA award from FRAXA board members Katie Clapp and Mary Beth Busby

FRAXA Research Foundation

Member Update

This newsletter is published quarterly and sent to all members of FRAXA Research Foundation.

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PLEASE JOIN **FRAXA Research Foundation**

IN SUPPORTING RESEARCH AIMED AT
TREATMENT FOR FRAGILE X

FRAXA is a national 501(c)(3) tax-exempt organization. You can join for a tax-deductible donation of \$25 or more per year. Every penny you donate goes to research: FRAXA has specific grants to cover all overhead. Members receive this quarterly newsletter and are welcome to participate as active volunteers.

Yes, I would like to join FRAXA

- Member (\$25+) Benefactor (\$500+)
 Donor (\$50+) Research Underwriter (\$1000+)
 Sponsor (\$100+) Named Research Fund (\$5000+)
 Named Research Chair (\$25,000+)



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FRAXA UPDATE

SUMMER 1999

VOLUME 6, NO. 2

A PUBLICATION OF
FRAXA RESEARCH
FOUNDATION

"**N**EVER DOUBT
that a
small group of
thoughtful,
committed
citizens can
change the
world.

INDEED, IT'S
the only
thing that
ever has."

— Margaret Mead

Fragile X Research Breakthrough Act of 1999 Introduced in Congress

Over the past few years, many of you have written or called your representatives in Congress to support increased funding for fragile X research. Now, because of all of our collective efforts, a major bill for fragile X funding has been introduced into both Houses of Congress. If passed, this bill will provide:

- **\$10 million per year to fund at least three fragile X research centers and**
- **\$2 million per year to encourage health professionals to conduct fragile X research by repaying a portion of their educational loans.**

On April 15th, Congressmen William Delahunt (Democrat, Massachusetts) and Wes Watkins (Republican, Oklahoma) introduced H.R.1445, The Fragile X Breakthrough Act of 1999. On May 26th, Senators John Edwards (Democrat, North Carolina) and Chuck Hagel (Republican, Nebraska) introduced an identical "companion" bill in the Senate, S.1131. Our task now is to persuade other members of Congress to sign up as "co-sponsors" of H.R. 1445 and S.1131. Please write, call or visit your Senators and Representatives and ask for their support!

Turn to page 2 for details.

NEW RESEARCH GRANTS FUNDED

In June, FRAXA's Board of Directors awarded over \$500,000 in new research funding for the coming year. Six new projects were funded, and seven others were renewed or expanded. FRAXA is now funding twenty top-notch FRAXA-funded teams at universities around the world, who are attempting to solve the puzzle of fragile X. Descriptions of current research follow.

See page 4 for Research Projects

Also in this issue:

- New members join FRAXA's Scientific Advisory Board
- FRAXA receives million dollar donation
- New chapters kick off, from Alaska to Florida

This is an extraordinary time for FRAXA and for everyone touched by fragile X. Over the last few months, much has happened:

- A bill has been introduced in Congress to fund fragile X research centers.
- FRAXA funded 6 new research projects and renewed or expanded 7 more.
- Fundraiser were held across the country!

Thanks to our growing team, we are making wonderful progress. Let's keep the momentum going!



Clockwise from above:

Philadelphia Gala, page 6

Roger Mudd addresses attendees of the Mary Higgins Clark Gala, page 4

Winners of the 1999 Patrick's Pals Tournament, page 6



FRAXA is a nonprofit, tax-exempt private charity run by parents of children with fragile X syndrome. Fragile X syndrome is the most common inherited cause of mental retardation and developmental disabilities, affecting approximately 1 in 2000 males and 1 in 4000 females. FRAXA's goal is to accelerate research aimed at the treatment of fragile X, by direct funding of promising research projects and by raising awareness of this disease.

NEW RESEARCH GRANTS FUNDED

1. Transgenic Mouse Model of Fragile X Syndrome: Temporal and Spatial Restriction of FMR1 Expression in Mouse Forebrain

ERIC R. KANDEL, MD

Principal Investigator

DUSAN BARTSCH, PH.D.

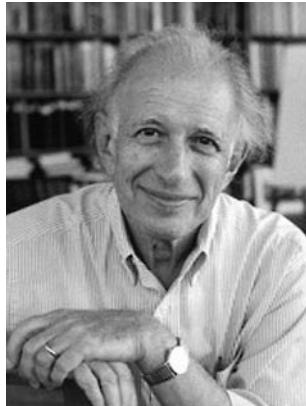
Postdoctoral Fellow

Columbia University

\$150,000/year for 2 years

by Eric Kandel

Fragile X syndrome is the most frequent inherited cause of mental retardation.



Dr. Eric Kandel

Fragile X pathology is linked to the alterations of the FMR1 gene encoding the FMR1 protein. Our aim is to develop genetically modified mice that would enable us both to explore the role of FMR1 gene and its protein product FMRP in neuronal function and in the cognitive defects of fragile X syndrome. By this means we have to facilitate the development of therapeutic approaches to fragile X.

To develop effective approaches to therapy, we need to determine the developmental time window during which the absence of the FMR1 protein damages brain function. Does the damage occur prenatally or postnatally? If fragile X defects are induced in brain prenatally, during development, can the damage be reversed by reactivating the gene postnatally? What is the optimal and necessary time window for the gene reactivation to restore cognitive function? In which parts of the brain has the FMR1 gene been activated to restore the function? To address these questions, we propose to develop two new types of genetically modified mice:

First, we will develop a mouse with the FMR1 gene specifically ablated (knocked out) in the forebrain using the cre/lox P system. This restriction of the knockout will allow us to study specifically the role of the FMR1 gene and its product FMRP in those brain structures associated with higher cognitive function, without the complicating effects of FMR1 gene knockout in other tissues.

research

Second, in a complementary approach, we will generate transgenic mice with tetracycline inducible, temporally and spatially regulated FMR1 expressed in the mouse forebrain. We will use these transgenic mice in conjunction with the already existing complete FMR1 knockout mice to study the role of FMR1 protein in the brain areas implicated in higher cognitive functions and learning and memory with high temporal and spatial specificity. We plan to use both these mice to evaluate the potentials of demethylation therapy and gene therapy.

Dr. Kandel is a recipient of the Lasker Prize, second in prestige only to the Nobel Prize. He has recently become interested in studying fragile X syndrome. Dr. Kandel has also agreed to serve on FRAXA's Scientific Advisory Committee.

2. Characterization of Transgenic Fragile X "Rescue" Mice

FRANK KOOY, PH.D.

Principal Investigator

ILSE GANTOIS

Graduate Student,
University of Antwerp
\$30,000

by Katie Clapp

Much of the recent research funded by

FRAXA has focused on fragile X knockout mice. These animals are normal except that they lack the fragile X gene (FMR1). Like most humans with fragile X, the knockout mice do not produce the protein FMRP, potentially involved in normal learning and memory. The mouse model is critical to research because potential treatments can be tested in the animals. However, better behavioral, cognitive, molecular, and neuroanatomical tests are needed to distinguish between normal mice and fragile X knockout mice.

Dr. Kooy's team will use the knockout mouse to investigate whether gene therapy could be an effective treatment or cure for fragile X. In collaboration with Cathy Bakker and Ben Oostra (Erasmus University, Rotterdam, the Netherlands), he will introduce a functional fragile X gene into the mouse genome using genetic engineering techniques. He will then compare these "rescued" mice with fragile X knockout mice, at several stages of development, by looking at: 1) phenotype (macroorchidism), 2) performance in a variety of behavioral and cognitive function tasks, including the Morris water maze test, 3) abnormalities of dendritic spines in neurons, and 4) gene expression profiles of genes differentially expressed between fragile X knockout mice and control littermates.



Edwin Reyniers, Ilse Gantois, Dr. Frank Kooy

OUR SCIENTIFIC ADVISORS

FRAXA encourages researchers from all over the world to submit applications to support their work aimed at finding an effective treatment or cure for fragile X syndrome. Twice each year, FRAXA's Scientific Advisors review proposals and make recommendations to the Board of Directors. The Board then votes which grants to award, based on the views of the experts and available funds. The process is fast and effective, thanks to our advisors, who graciously volunteer their time to review applications:

W. Ted Brown, M.D., Ph.D. Professor and Chairman, Department of Human Genetics Institute for Basic Research in Developmental Disabilities Staten Island, NY

Robert Bauchwitz, M.D., Ph.D. Research Scientist Department of Genetics and Development Columbia University, NY

William Greenough, Ph.D. Professor of Psychology and Neuroscience, Beckman Institute University of Illinois at Urbana-Champaign, IL

David Gwynne, Ph.D. Senior Director of Biotechnology, Cambridge NeuroScience Inc., Cambridge, MA

Randi Hagerman, M.D. Professor of Pediatrics and Director Fragile X Treatment and Research Center, The Children's Hospital, Denver, CO

Eric Kandel, M.D. University Professor, Center for Neurobiology & Behavior, Columbia University, NY and Senior Investigator, Howard Hughes Medical Institute

Charles Laird, Ph.D. Professor, Genetics, Fred Hutchinson Cancer Research Center, University of Washington Seattle, WA

Herbert Lubs, M.D. Professor of Pediatrics and Genetics, Univ. of Miami School of Medicine, FL

Pamela Mellon, Ph.D. Professor, Department of Reproductive Medicine and Neurosciences, Univ. of California at San Diego

David Nelson, Ph.D. Professor of Molecular and Human Genetics, Baylor College of Medicine, TX

Ralph Nitkin, Ph.D. Bethesda, MD

Owen Rennert, M.D. Professor Emeritus Division of Genetics, Dept. of Pediatrics, Georgetown University, DC

MILLION DOLLAR GIFT

This Spring, FRAXA received a wonderful gift from a family which has supported our cause for several years. Lester and Frances Johnson of Wisconsin have contributed over one million dollars to FRAXA Research Foundation. Fragile X research is very important to Mr. and Mrs. Johnson, as it is to all of us. We are very grateful to the Johnsons for enhancing our ability to support research aimed at finding a treatment for fragile X.

"We expect that fragile X research will affect changes for future generations as well as bring hope soon to fragile X families." – Frances and Lester Johnson

Why Fund? *continued from back cover*

approaches to treatment and even cure for many disorders.

In 1991, an international effort led to the identification of the genetic abnormality in fragile X, a mutation in which three letters of the genetic code are repeated an abnormally large number of times. This "trinucleotide repeat expansion" represented a novel type of mutation that has since been found to cause many other important genetic diseases affecting brain function, including Huntington's disease, myotonic dystrophy (the most common form of adult muscular dystrophy), and a number of other progressive neurodegenerative diseases. Fragile X research led the way for recognizing the genetic basis of the other diseases, and it now serves as a model for understanding why the genetic abnormality causes disease. This last point is critical for the establishment of effective therapies; for none of these diseases is an effective treatment now available. However, for fragile X, there is reason to be optimistic, since the gene itself is normal, but is just switched off by the mutation. Thus, simply switching the gene on again may provide an effective approach to treat or even cure the disease. Experiments aimed at turning on the gene are beginning in the United States and Europe.

Support for fragile X research and treatment centers should prove to be a cost-effective alternative to current maintenance therapies. The average cost of lifetime care for a single, severely affected individual with fragile X is 2 to 5 million state dollars, and there are approximately one-hundred thousand affected individuals in the United States. Thus, for fragile X alone, an effective therapy would result in an immense cost savings. Moreover, the information gained through combined molecular/clinical research in fragile X will address many of the same issues in mental retardation and autism, and should provide important clues for understanding the neurodegenerative disorders such as Huntington's and myotonic dystrophy.

Report from Washington

This is a His and Hers letter. Mary Beth writes about the Gala, which by now is "history;" and David's writes about Lobby Day and the Congressional bills, with which we hope to make history. David Busby writes:

There is lots going on, now that the Fragile X Breakthrough Act of 1999 has been introduced into Congress. This marks an opportunity for us all to work together to persuade Congress that fragile X research merits increased funding, because of the prevalence of fragile X and the promise this research holds for other diseases and disorders. Through the National Institutes of Health (NIH), (and using your tax dollars), Congress controls about half of all U.S. medical research funds spent each year.

SETTING THE STAGE

The morning after FRAXA's very successful Gala (see elsewhere), we held a Lobby Day. About 45 gallant parents, siblings, and friends attended the "kick-off" breakfast, and, armed with materials, fanned out over Capitol Hill to ask their members of Congress to increase NIH support for Fragile X research. In June, Representatives Delahunt and Watkins, together with FRAXA, sponsored a Congressional Briefing breakfast for members of Congress and their staffs. Co-sponsors of H.R. 1445, Bill Delahunt, Wes Watkins, and Bill Barrett (R.Neb.) spoke enthusiastically about the bill. Dr. Felix de la Cruz, Chief, Mental Retardation Branch of the NICHD, spoke of the importance of Fragile X research. Dr. Randi Hagerman described fragile X symptoms, showed slides of families, and made it clear how common it is. Dr. Paul Hagerman explained current research efforts and why Fragile X research could lead to progress in research on many other diseases. Jack Busby (who has Fragile X) and Kathy May (a mom and terrific advocate) discussed Jack's job and life in a group home. It all went very well. After the briefing, Mr. Delahunt and Mr. Watkins gave us valuable insights into how we can make fragile X real to members of Congress. We were particularly pleased that the key staffers of Senators Edwards and Hagel, Laurie Armstrong and Stephen Irizarry, attended and will help us put on a similar briefing on the Senate side soon.

A CALL TO ACTION

Now that the Fragile X Research Breakthrough Act of 1999 is official, our main task is to sign up co-sponsors for H.R.1445 in the House of Representatives and S.1131 in the Senate. So far, FRAXA families have contacted over 100 congressional offices. These bills are being noticed: a staff member from Senator Hagel's office said "We've gotten more mail on this issue than on Medicare!" All that mail was generated by one family –and all their friends, neighbors, car mechanics, teachers, etc. etc. THANK YOU Megan Massey and the Hamsa gang!!! Keep up



the "drum beat" by meeting with, calling, writing, and emailing your Representatives! Please let me know their responses [New Address: David Busby, Dorsey and Whitney, Suite 300 South, 1001 Pennsylvania Avenue, Washington, D.C. 20004 or e-mail: busby.david@dorsey-law.com]. Roger Hoh of Houston deserves special mention. He and his friends have contacted the entire – and powerful – 32 member Texas Delegation. Roger's letter is a good model to follow. (See below.) Also with stars in their crowns are North Carolina's Dr. Don Bailey, who found our first Senate sponsor, Senator William Edwards and Nebraska's Hamsas, who convinced Senator Hagel to be an original sponsor of our cause and signed up every Nebraska Senator and Congressman as co-sponsors!

Please be warned: this begins a long journey. The legislation must be passed by both houses of Congress and signed by the President. The appropriations to fund it must similarly pass through both houses and be signed. Most bills take years to become law, if they succeed at all. If ours becomes a law during the 106th Congress, it would be a miracle – but then, we're into miracles.

Meanwhile, we'll push hard for current NIH support. We hope to get language in both

*"We've gotten
more mail
on this issue
than on
Medicare!"*

– Steve Irizarry
Staff, Senator Hagel

Senate and House Appropriations Committees' Reports, asking the NIH's National Institute for Child Health and Human Development (NICHD) for additional funding of fragile X research during Fiscal Year 2000. Language in support of fragile X has been in previous reports, and, as the figures will show, it has helped:

Spending on Fragile X Research, by the National Institute of Child Health and Human Development (NICHD)	
FY 1994	\$1,860,234
FY 1995	\$1,893,663
FY 1996	\$1,807,608
FY 1997	\$3,628,000
FY 1998	\$4,329,386

(source: NICHD)

Now is the time – whether you have done so or not – to visit or write your Senators and Representatives – to ask them to co-sponsor S. 1131 or H.R. 1445 – to urge them to write colleagues on the Senate and House Appropriations Committees requesting enhanced funding by the NIH for fragile X research in Fiscal Year 2000.

MORE INFORMATION:

Details on H.R.1445 and S.1131 are available on the web at:

<http://www.fraxa.org>

Sample letters to your reps are here as well.

<http://thomas.loc.gov>

Search for "fragile X", and then click on "Bill Summary and Status" to see who has co-sponsored so far. This site also has names and addresses of all members of Congress.

You will find names and addresses of all members of Congress at <http://clerkweb.house.gov/mbrcmtee/mbrcmtee.htm>

Send a letter to any senator at:

Senator _____, Senate Office Bldg., Washington, DC 20510

or to House members at:

The Honorable _____, House Office Building, Washington, DC 20215

or call the Capitol, and ask for your senator or representative: **202-224-3121**.

WASHINGTON, D.C. GALA

by Mary Beth Busby

I hope that all 300 of you who were at the 2nd Annual Mary Higgins Clark Gala on April 19th, here in Washington, enjoyed it and felt that it constituted a plus for FRAXA. It was indeed a financial plus, raising \$262,000. We were able to hold our expenses down to \$38,491.67. This leaves us with about \$223,000 to put straight into research. Our boundless gratitude goes to Mary Higgins Clark for coming, for speaking so movingly and graciously, and for just being her wonderful self. We have many blessings to count here in Washington – despite what you may read in the newspapers. I think the FRAXA dinners, both this year and last, generated a rather special spirit, in that every single person there knew someone who is either affected or a carrier – almost a magic circle. In addition, everyone who talked to me afterwards said that they actually learned something – a rather unique experience at Washington fundraisers.

We were very proud and honored that Donna Shalala, Secretary of Health and Human Services, chose to attend our gala. Thanks to Kitty and Enzo de Chiara, Hillary Clinton taped a video, shown at the beginning of the dinner. She truly hit



Mary Higgins Clark
Mary Higgins Clark



Mary Higgins Clark

all the right buttons, and it was outstanding. Thank you, Kitty and Enzo, for that and so much more. Thanks, too, to my wonderful co-chair and dear friend, Diane Rehm, who was with me every step of the way. Our host for the evening, Roger Mudd, a caring, generous friend, caught the moment with his customary reporter's instinct. Bishop Jane Holmes

Dixon gave an inspiring invocation, reminding us all of our many blessings, as well as our challenges. Jim and Sylvia Symington added the after-dinner fun with their world-class entertainment. A big acknowledgment goes to our special Benefactors, Patrons, and Sponsors: Debbie and Jeffrey Stevenson, Bristol-Myers Squibb, Cipriani, Simon and Schuster, Schering-Plough, Pfizer, Bell Atlantic, Ellen Atwell, and Mary Higgins Clark. Finally, there could have been no dinner without the Gala Committee, which came out in full force to support this event. We can never thank you all enough.

We're all thrilled that the Chicago FRAXA group has embraced the challenge of doing the Gala next April 30th (a Sunday night). Jay and Joan Canel have chosen the Four Seasons Hotel in Chicago. The Four Seasons did a grand job of making this year's event the event we wanted; that's the kind of organization it is. Mrs. Clark has already put the date on her busy calendar. So the 3rd Annual Mary Higgins Clark Gala is already off on the right track. Let's all get the Chicago event on our calendars for 2000 and turn out in support.



Jack and David Busby who both have
fragile X syndrome

unusually abundant and tend to have relatively immature forms, similar to what may be seen in the brains of infants. We do not know, however, whether these structural changes in dendritic spines are directly responsible for symptoms of fragile X. This is an especially difficult question to address since dendritic spines can change in size and shape over the course of minutes. Since this motility might itself be a structural manifestation of the biochemical changes that take place with thought processes such as learning and memory, it is important to know how it changes during normal brain development and how it is affected in disorders such as Fragile X syndrome.

The studies we propose are designed to uncover the changing nature of dendritic spine motility as an animal grows from infancy to the equivalent of childhood, and then to discover how this motility during this crucial period is affected in the knockout mouse model of Fragile X syndrome. Finally, if a disorder is detected, we propose to reintroduce the missing gene directly into individual neurons and determine whether this single manipulation is sufficient to correct the earlier-described disorder.

In order to carry out these studies, we will label neurons with a brightly fluorescent protein by infecting them with a harmless virus carrying the gene for the marker. This marker, enhanced green fluorescent protein (EGFP), fills the entire neuron, even the spines, with a bright green label. Using a special custom-designed microscope, neurons filled with this label can be visualized at very high magnification while still in the intact, living animal. The use of this technology (two-photon laser scanning microscopy) offers numerous advantages, especially very minimal damage to the animal and the ability to visualize neurons well below the brain surface. Thus neurons involved in a given pathway (in our case, in the part of the sensory system responsible for sensation using the whiskers) can be observed repeatedly over extended periods of time in normal and fragile X animals at different ages. Finally, the same virus used to introduce the fluorescent marker can be used to introduce, at the same time, the FMRP that the animals lack, rendering bright green only those neurons whose genetic defect has been "corrected." The effects of reintroduction of the gene can then directly be studied with the same imaging system described above. We hope that this approach to studying Fragile X syndrome will contribute significantly to our understanding of the way the normal brain develops, as well as to how a single genetic defect can so profoundly affect cognitive function.

6. Localization of RNA binding proteins to dendrites and spines: its possible role in synaptic plasticity.

GARY BASSELL PHD Principal Investigator

D. TIRUCHINAPALLI PHD Postdoctoral Fellow

Albert Einstein College of Medicine, \$30,000

by Katie Clapp

Dr. Bassell and Dr. Tiruchinapalli will use state-of-the-art visualization techniques to further define the role of FMRP in the dendrites and spines of rat hippocampal neurons. They will fuse FMRP with GFP (green fluorescent protein) and correlate that protein with the positions of other proteins and mRNAs in the dendrites, in response to various externally applied compounds (such as growth factors and various drugs) and during long-term potentiation. Other neuronal proteins and mRNAs will also be visualized. Some of this will be possible in living sections, other aspects will be done in cell cultures. This work is important for understanding the broader role of FMRP in neuronal function and behavior.

RENEWALS AND EXPANSIONS:

7. Restoration of Natural FMR1 Expression by PAC Transgenesis (RENEWAL)

**ROBERT BAUCHWITZ,
M.D., PH.D.**

Principal Investigator
Columbia University, \$35,000

by Katie Clapp



Much exciting current research aims to use gene therapy techniques to reintroduce the missing FMR1 gene into neurons of the fragile X knockout mouse. One of the challenges of gene therapy is to introduce a new gene (transgene) into cells in such a way that the transgene functions precisely like the normal gene, producing the right amount of its protein product, FMRP. This is no easy task, because genes are regulated by large sequences of DNA, and it is not yet understood which of these sequences are critical for proper functioning of the FMR1 gene. In addition, the mouse FMR1 gene is not exactly equivalent to the human FMR1 gene, so mouse studies may be complicated by these differences.

The goal of this project is to find the smallest piece of DNA (the FMR1 gene and regulatory sequences) that is necessary for the gene to function properly. Using gene therapy techniques, Dr. Bauchwitz has introduced the entire human FMR1 gene with all needed regulatory sequences into the mouse embryo. These transgenic animals are currently being analyzed to ensure that the introduced gene is functioning as expected. The next step is to pare away at this large piece of DNA (which is too large to be introduced cleanly into neurons) to determine which regulatory

continued on page 11

update.

3. The Molecular Mechanisms Mediating Mental Retardation in Fragile X Syndrome

ALCINO SILVA, PH.D.

Principal Investigator

PAUL FRANKLAND, PH.D.

Postdoctoral Fellow, UCLA, Los Angeles, CA

by Alcino Silva



Dr. Silva

Our laboratory is studying mechanisms of learning and memory. We are interested in uncovering how memories are established in the brain, the molecules involved and the brain processes mediating this magical phenomenon. We believe that the gene disrupted in Fragile X plays an important role in these processes, and we would like to determine the exact mechanism by which this mutation results in learning impairments. A few years ago, we discovered that the CREB protein is required for memory in mice. This protein is also thought to be required for memory in humans. Mice with deficits in this protein can learn but they are unable to retain for more than a few hours the learned information. We suspect that the CREB protein may regulate the protein disrupted by the fragile X mutation. The FRAXA grant will enable us to test this hypothesis. Most of our studies will be done with mutant mice. These mice are essential models of the human disease because many of the crucial experiments cannot be done with patients. The mice allow us to test key hypotheses, and hopefully in the near future, they will also allow us to evaluate potential cures.

4. Molecular Mechanisms of Fragile X Syndrome: Characterization of FMR1 and the FXR Proteins

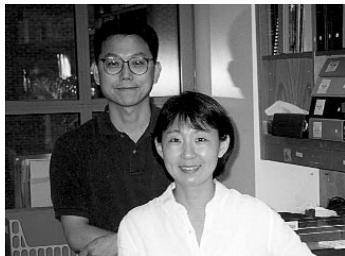
HARUHIKO SIOMI, PH.D.

AND MIKIKO SIOMI, PH.D.

Principal Investigators

Tokushima University, Japan, \$70,000

by Haruhiko Siomi



Our genes make up the scaffolding upon which proteins are created. Each gene encodes for an "alphabet" that encodes for thousands of proteins. Many fragile X patients either fail to make the protein product of the fragile X gene, FMR1, or make an ineffective mutant version of it. In order for a protein to be produced,

another chemical, RNA, must be created upon the DNA scaffolding of the gene. RNA is the cell's workhorse: it copies the genetic message off DNA and takes it out to the cellular factories (ribosomes) where the encoded message dictates the assembly of a protein. In normal cells, the FMR1 protein can bind RNA and is associated with ribosomes.

Interestingly, in our cells, there are two genetic "cousins" of FMR1, termed FXR1 and FXR2, which are thought to team up with and work together with FMR1. The current hypothesis is that the FMR1 and FXR proteins bind to specific messenger RNAs and regulate expression of those RNAs at ribosomes (protein assembly factories) in a manner critical for correct development of neurons in the brain. One of our goals is to sort through the thousands of RNAs that brain cells make and find the particular RNA that the FMR1 protein binds to. In order for this to be achieved, we plan to manipulate cells in such a way where they fail to make FMR1 and/or FXRs. We then will compare the expression of RNAs at ribosomes in cells that make the FMR1 and FXR proteins and the expression of RNAs in cells which fail to make these proteins. Once we elucidate these differences, we can effectively begin to address the question of how the lack of FMR1 expression (or the expression of mutated version of FMR1) leads to symptoms in fragile X syndrome.

Drs Haruhiko and Mikiko Siomi are relocating from the University of Pennsylvania to Japan where they have tenured faculty positions and, with the FRAXA grant, will hire two postdoctoral fellows.

5. Imaging of Neocortical Dendritic Spine Maturation in FMR1 Knockout Mice Using Two-Photon Laser Scanning Microscopy

KAREL SVOBODA, PH.D. Principal Investigator

ADAM OBERLANDER

Technician, Cold Spring Harbor Laboratory, NY,
\$30,000

by Karel Svoboda



Adam Oberlander, Esther Nimchinsky, Karel Svoboda

One of the most interesting features of the fragile X syndrome is the apparent involvement of dendritic spines. These tiny appendages stud the surface of most neurons in the cerebral cortex, and are the sites where these neurons receive most of their inputs. As a result, they play a pivotal role in the communication between neurons. It is perhaps not surprising, therefore, that in several forms of mental retardation, these structures are somehow altered. In Fragile X syndrome, they are

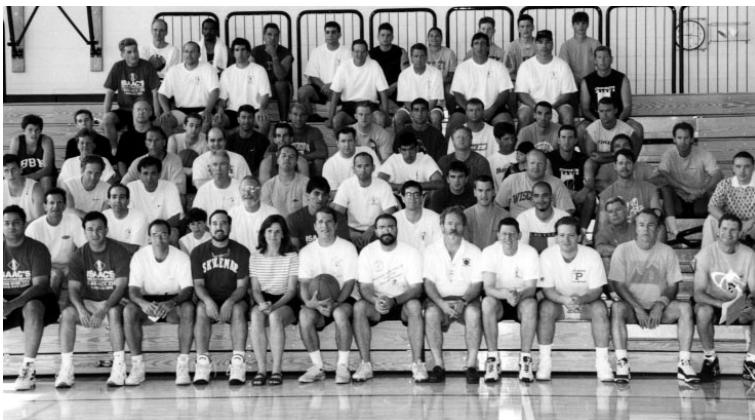
Research Update continued on page 10

More FUN-draisers

PATRICK'S PALS

The Third Annual Patrick's Pals Basketball Tournament was held in June, in Cambridge, Massachusetts. Jimmy and Pamela Vershbow's good friends Jimmy Marks, Steve Savarese, Billy Rome and John Pressman organized a slam dunk tournament. Over 40 teams faced off, and about \$15,000 was raised for FRAXA. Sadly, neither Jimmy nor Pamela could join us at the tournament. Pamela wrote: "We are very sorry to be missing this day, but for the past 11 days our 6-year-old son Patrick has been in and out of the hospital because he stopped drinking. Part of fragile X syndrome is a strong dependence on routines. So, when Patrick's bottle broke and he needed to use a new one – he refused . . . not through stubbornness, but due to a real fear about something new. Patrick became so dehydrated he needed IV fluids; this week he was brought to the hospital three times for hydration. Finally, we had to admit him to the hospital to monitor his health and to try to help him start drinking again. We are still at the hospital now, on the day of the tournament. This heightened anxiety and abnormal behavior is just one of the aspects of fragile X that needs more research; Patrick's current difficulties serve as a reminder of why we have this tournament, why raising money for research is so vital, and why every one of your contributions to FRAXA is so appreciated."

Editor's note: Patrick stayed in the hospital for several weeks. He is at home now. Our hearts and hopes are with him.



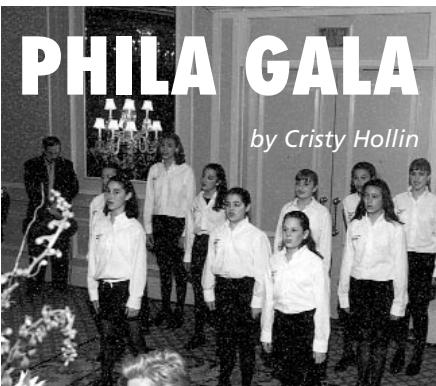
Philadelphia's Second FRAXA Fundraiser was stellar, raising over \$126,000! Held at the Ritz-Carlton Hotel on May 6th, it was an evening of elegance, warmth, and emotion. The theme of the evening, "It takes a village to raise a child," rang true as guests readily stepped up to support our cause.

The event included piano music, cocktails, and a lavish supper. We held a raffle and auction, the grand prize being a cruise for two to Tahiti, generously provided by The Travel Company. Nancy Glass, former host of American Journal, kicked off the evening by reminding guests that every time they go to a movie, they might be sitting next to a carrier of fragile X. Katie Clapp spoke of the efforts to find a treatment or cure for fragile X. Next, Mitchell and I, chairs of the event, welcomed and thanked our generous guests. Many were moved to tears, and others to cheers, by a video about our 6-year-old son, Matthew, and the research currently being funded by FRAXA. Finally, the children's choir The Triple Threat Vocal Forte stole the show.

We thank Stephen and Helene Kendall who provided major support for this event. We also thank our other underwriters: Mellon Private Asset Management, The Abramsom Family Foundation, Ellen and Ray Goldberg, Conservest Capital Advisors, Inc., Robin and Jerry Batoff, Sue and Sid Friedman, Elaine and Sidney Grobman, Sally and Harvey Kane, Sandy and Harvey Lamm, Natalie and Warren Werbitt, Joe and Joan Firestone, Dawn and Don Paperone, and Rosanna and Arthur Keyser. We also wish to thank our Village Mayors, Stephen and Helene Kendall, and Marjie and Lewis Katz, for their substantial contributions to FRAXA; our co-chairs and parents, Sylvia and Billy Bell and Sande and Harris Hollin for their tremendous support of our efforts.

Finally, we thank those who donated goods and services: Dan Brody Photography, Gargoyle Communications, Triple Threat Vocal Forte, Peter Scott Ruben Orchestras, Hope's Cookies, David Steerman, Elite Sportswear Products, Clinique, Arpeggio Restaurant, Margolis Wines and Spirits, Lynn Schreiber, Fresh Fields, Lafayette Hill Studios, Ritz-Carlton, Goldenberg's Peanut Chews, Simon and Schuster, Baby Bundles, Ultra Hardware Products, and Wendy Davis.

Finally, thanks to my committee for your time, effort, love and support. You're my village, and I couldn't have done it without you.



by Cristy Hollin

Above: Triple Threat Vocal Forte perform

Below: Gala attendees watch video presentation



Research Update continued from page 10

sequences are required for proper function of the gene. The hope is that this work will pave the way for treatment through gene repair or gene therapy.

This grant is an expansion of an ongoing project to support hiring a technician and for animal care and equipment costs.

8. Investigation of the Regulation of the Expression of the FMR1 Gene

WILLIAM T. GREENOUGH, PH.D.

Principal Investigator

ANDREA BECKEL-MITCHENER, PH.D.

Post Doctoral Fellow

University of Illinois, Urbana-Champaign \$30,000

by Andrea Mitchener



Andrea Mitchener

Our research is aimed at understanding the regulation of the FMR1 gene in order to identify sequences within the gene that are necessary for its proper expression. We will pursue the identification and investigation of regulatory regions contained within the FMR1 gene using two distinct, but related, approaches. The first is to continue ongoing studies into the "rescue" of the deleted gene in knockout mice. In collaboration with Dr. Robert Bauchwitz, the deleted FMR1 gene in the mouse has been replaced with a large sequence of the human FMR1 gene. Continued analysis of these animals is essential in order to gain an understanding of the extent to which this transgene allows for proper FMR1 gene expression *in vivo*. The second approach will use molecular biology techniques and cultured cells to study defined sequences within the promoter that drives expression of the FMR1 gene. These experiments are distinct from previous studies, which have emphasized the analysis of the unstable CGG repeats contained in the defective promoter. Instead, our research will focus on characterizing regulatory elements within the context of a functional gene. These complementary research strategies aimed at understanding normal FMR1 gene expression have relevance to both gene replacement therapies and to the eventual development of therapies designed to reactivate the disrupted gene.

9. Mechanisms Regulating Synaptic Protein Translation and a Search for Differential Synaptic Protein Synthesis in FMRP Knockout and Wildtype Mice

WILLIAM GREENOUGH PHD Principal investigator, U of Illinois

FRANK ANGENSTEIN MD Postdoctoral Fellow, \$42,000 (RENEWAL)

In an extension of previous FRAXA-funded work, this group is continuing to elaborate the precise molecular

cascade involving FMR protein following synaptic activity and, specifically, looking for proteins whose expression patterns are significantly altered when FMRP is absent.

10. Psychopharmacologic Studies of Fragile X (RENEWAL)

RANDI HAGERMAN, M.D. Principal investigator

KAREN RILEY, PH.D.

Postdoctoral Fellow, Children's Hospital, Denver \$30,000

11. Psychophysiological Measures of Arousal: Documentation of Treatment Effects & Impact of Disability (RENEWAL)

DON BAILEY, PH.D. AND MARIA BOCCIA, PH.D.

Principal Investigators, U of North Carolina

JANE ROBERTS, PH.D. Postdoctoral Fellow, \$30,000

12. The Role of Fragile X Related Genes in Mental Retardation and Neuronal Development (RENEWAL)

DAVID NELSON, PH.D. Principal Investigator

LAURA KIRKPATRICK, PH.D.

Postdoctoral Fellow, Baylor University, TX, \$30,000

13. Restoring FMRP Expression in Cells from Fragile X Patients (RENEWAL)

ANDRE T. HOOGEVEEN, PH.D., Principal Investigator,
Erasmus University, Rotterdam, The Netherlands, \$30,000

Additional research projects are also underway. Contact FRAXA for a complete list.

RESEARCH NOTICES:

NEW DIAGNOSTIC TEST

Please note that we have added the new test to identify fragile X patients by hair root analysis on our web-site:

<http://www.eur.nl/fgg/ch1/fragx/robwillemse>

SLEEP STUDY

Dr. Randi Hagerman's team in Denver, Colorado is currently conducting a two-part sleep study involving melatonin, funded by FRAXA. If your child is currently exhibiting difficulties falling asleep or waking up in the

conntinued on page 7

FRAXA CHAPTER NEWS

FEATURED CHAPTER NEWS

Our team now includes over 2400 advocates and supporters, and new FRAXA chapters from Alaska to Florida! A complete chapter listing is available from FRAXA or on the web.

Please send in your news or call to explore ideas for growing your chapter or starting a new one. Contact Katie Clapp at:

FRAXA Headquarters
45 Pleasant Street
Newburyport, MA 01950
Phone: (978) 462-1866
Fax: (978) 463-9985
www.fraxa.org
email: kclapp@fraxa.org

ALASKA NEW CHAPTER!

Wendy Cloyd
2148 Old Stease Hwy.
Fairbanks, AK 99712
wendyc@mosquitonet.com

Wendy is starting a new FRAXA chapter in Alaska and would like to connect with other families in the state.

ILLINOIS

Under the able leadership of Linda Canel, the Chicago FRAXA group's Bowling fundraiser raised over \$15,000! The kids had a blast bowling and consuming hundreds of slices of pizza and gallons of pop. Thank you Gail Borgerd, Pam Caplan, Cherie Dodson, Karen Dorfmeyer, Jody Goldsmith, Laura Palmere, Diane Panzeca, Avis Primack, Bev Romanoff, Maureen Schmidgall, Sarah Urycki, and all the members and guests who made the day such a success!

Upcoming Chapter meetings are scheduled for Saturday afternoons, July 24th, August 28th, September 25th, October 23rd, and November 27th. Contact Jody for more information.

FLORIDA

NEW CHAPTER!
Leigh and Frank Vadala
182 B Boundary Blvd.
Rotonda West, FL 33947
(941) 697-3798
beanfiend@ewol.com

Contact Leigh if you are interested in joining our newest Florida chapter in the Tampa Bay area.

Thanks to Martha Matthews, the city of Fort Walton Beach declared April 13, 1999 to be Fragile X Awareness Day.

MASSACHUSETTS

Please welcome Sandy Morse who is now running FRAXA's Mass. Chapter.

Contact Sandy at Family TIES, N.E. Regional Health Office, Tewksbury Hospital, Tewksbury, MA 01876
Phone: (978) 851-7261
email: OldeMissy@aol.com

Sandy leads monthly support group meetings at Tewksbury Hospital.

NEBRASKA

John and Megan Massey
90473 28th Avenue
Scottsbluff, Nebraska 69361
(308) 635-7109 Email
meganm@ricochet.net

I am in the planning stages of kicking off the Nebraska FRAXA chapter. If there are any families



The Hamsa and Massey family at the FRAXA gala in Washington, DC

in Nebraska involved with Fragile X, please contact me. I live in Scottsbluff, 30 miles from the Wyoming border and 450 miles from Omaha. I have only found three other families in the state who are raising children with fragile X. We hope to have had a couple of fundraisers by this time next year.

I had the opportunity to attend the Fragile X Benefit Gala in Washington, D.C. - with an entire table full of sisters, cousins and aunts!

Having never been to D.C., I can truly say it was an experience I will never forget. My mother, Diane Hamsa, who is from Omaha, and I spent a whole day in D.C. lobbying on Capitol Hill for Fragile X and trying to obtain support for H.R. 1445, The Fragile X Breakthrough Act of 1999. I am pleased to report our own Senator Hagel from Nebraska was instrumental in cosponsoring the Senate companion bill to H.R. 1445, now known as S.1131. It was with his help and Senator Edwards from North Carolina that this bill was introduced. We also met with the other Representatives from our state. All of the Nebraska Congressmen and both Senators have signed on as cosponsors to H.R. 1445 and S.1131 - we have a grand slam for Fragile X in Nebraska! I have really enjoyed working

with the FRAXA people. They are truly a professional group of citizens and I am proud to be a part of their group.

NEW YORK

NEW CHAPTER!

Debbie Stevenson
1021 Park Ave., Apt. 6B20
New York, NY 10028-0959
(212) 828-1883 or
(917) 226-9021

I am happy to announce that I will be starting a New York City Chapter for FRAXA. My goals are to help those who need information locally and to raise a bundle of money so that FRAXA can have future events to raise cash for other causes since this one will have been cured. If you would like to participate in any way in a fundraiser that will take place in the spring, please let me know. Thanks!

NORTH CAROLINA

NEW CHAPTER!

Steve & Teresa Strom, 5412 Pear Orchard Lane, Raleigh, NC 27616. E-mail: teresastr@aol.com
Phone: 919-981-0055
Fax: 919-954-9955

Steve and Teresa have a 2-1/2 year old affected son, Adam. They have been active with FRAXA for several years; they hope to raise both funds and awareness in the Triangle area.

TEXAS

Roger Hoh and Susannah Dickman attended the Texas Genetics Network (TEXGENE) Annual Conference in San Antonio. TEXGENE is a statewide consortium of individuals and organizations involved in providing genetic services or who represent people with genetic disorders or birth defects. During the Steering Committee meeting we asked that TEXGENE write letters in support of H.R. 1445 and S. 1131 to all 32 Texas delegates. This request was approved!

Research Notices *continued from page 11*

middle of the night, he or she might be appropriate for the study. If you are interested in participating in or finding out more about the study, please call Dr. Karen Riley at 303-764-8361.

PROJECT ON ADOLESCENTS WITH FRAGILE X SYNDROME

Funded by the National Institutes of Health and the University of Wisconsin at Madison, this project has two goals:

1. To understand more fully the nature of the problems in language and communication that affect many individuals who have fragile X syndrome; and
2. To learn more about the impact of having a son or daughter with fragile X on parents and other family members. I'm especially interested in providing more information to researchers, clinicians, and families about the issues and challenges that are unique to fragile X and that distinguish it from other conditions, such as Down syndrome.

We would like to include families that have a son or daughter with fragile X who is between the ages of 11 and 22. Participation requires one or two visits to the Waisman Center in Madison. We can cover limited travel expenses for families who must stay over night. Participating families will receive a report detailing their child's performance and will receive informational brochures and books. I can be contacted at: Len Abbeduto, Ph.D. Professor of Educational Psychology Waisman Center, University of Wisconsin-Madison Madison, WI 53705, (608) 263-1737 abbeduto@waisman.wisc.edu.

MATERIALS AVAILABLE:

FROM NICHD:

National Institute of Child Health and Human Development has published a free brochure on fragile X syndrome. This 12-page brochure is useful for educators and medical professionals as well as families. Up to 50 copies of this brochure can be requested from the NICHD Clearinghouse, P.O. Box 3006 Rockville, MD 20847, (800) 370-2943 Fax: (301) 984-1473 , 8:30 a.m. - 5:00 p.m. eastern time, Mon. - Frid. Or, order online at the NICHD website: <http://www.nih.gov/nichd>

FROM FRAXA:

FRAGILE X INFORMATION CARDS

These business-size cards fit in a wallet; many families have asked for a card that they can give to people who have no knowledge of fragile X. Cards are \$10 per 100.

HAVE YOU HEARD OF FRAGILE X?

Our loved one has Fragile X Syndrome

Fragile X is an inherited genetic disorder which affects 1 in 2000 boys and 1 in 4000 girls. It can cause:

- mental impairment ranging from learning problems to mental retardation
- behavioral challenges, like anxiety & hyperactivity
- autistic-like behaviors, such as hand-flapping

YOU CAN HELP
Please understand that new situations will cause our loved one to become anxious and afraid. Often, neither we nor (s)he can control this behavior. So please be encouraging and just *Smile!*

FOR MORE INFORMATION
FRAXA Research Foundation
45 Pleasant Street, Newburyport, MA 01950
web: <http://www.fraxa.org>

In December 1998, the National Institute of Child Health and Human Development (NICHD) and FRAXA co-sponsored a meeting of about 30 top scientists to chart the direction of future research on fragile X. A summary and recommendations resulting from the meeting were recently published, in the

American Journal of Medical Genetics ,

Volume 85, Issue 3, 1999

Special Issue: X-Linked Mental Retardation, Part III.

Issue Edited by Jeanette J.A. Holden. pp. 317-322

Workshop on fragile X: Future Research Directions,

by Edward R.B. McCabe, UCLA,

Felix de la Cruz, NICHD, and

Fragile X Articles

The Advocate 1995 - 1997 published by Avanta Media Corp. 173 pages \$25

A Medication Guide for Fragile X

by Michael R. Tranfaglia MD, Psychiatrist
Medical Director of FRAXA

This recently updated guide is intended to help parents and others understand behavioral symptoms of fragile X and the medications commonly prescribed to help manage these symptoms. Available from FRAXA for \$25; proceeds go to fragile X research.

**Updated FRAXA Brochures
and gift envelopes are
now available.**



Booklet available:

Fragile X - A to Z

Wendy Dillworth, FRAXA Michigan Chapter leader, has created a wonderful guide for families. Fragile X - A to Z is chock full of stories from daily life with fragile X children. Browse through helpful suggestions on topics such as adolescence, bike riding, computer software, and dental work. Wendy has collected these tips from the Fragile X Listserv with permission from each author. This 73-page soft cover guide is available from FRAXA for \$15 postpaid within the US; elsewhere please add \$5.

FRAXA POSTDOCTORAL FELLOWSHIPS REQUEST FOR GRANT APPLICATIONS

**Upcoming Deadlines: December 1, 1999
and May 1, 2000**

FRAXA offers fellowships and grants to encourage research aimed at finding a specific treatment and ultimate cure for fragile X syndrome:

- Postdoctoral fellowships of up to \$35,000 each per year
- Investigator-initiated grants for innovative pilot studies aimed at developing and characterizing new therapeutic approaches (no funding limit)

FRAXA is particularly interested in preclinical studies of potential pharmacological and genetic treatments for fragile X and studies aimed at understanding the function of the FMR1 gene. Applications are accepted twice each year. Information is available at www.fraxa.org or by contacting FRAXA.

WHY IS FRAGILE X RESEARCH WORTHY OF FUNDING?

To families, the answer is obvious. But fragile X research could help many others as well. Thanks to Paul Hagerman, MD, Ph.D. and Randi Hagerman, MD, for articulating why:

Fragile X is the most common inherited form of mental retardation: approximately one in 260 women carry a mutation in the fragile X gene, and about 1 in 2000 boys and 1 in 4000 girls are impaired by the disorder. Identifying the molecular basis of the fragile X syndrome is of pivotal importance for understanding a wide variety of genetic and non-genetic diseases that affect the brain. Fragile X is the leading form of autism with an identified molecular basis, and represents the best clinical model for investigating this often devastating disorder. Fragile X also causes a spectrum of other behavioral abnormalities, including hyperactivity, learning disabilities, mood instability, obsessive-compulsive behavior, and psychosis. Thus, fragile X represents a "portal" for understanding gene-brain-behavior connections and for developing rational

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FRAXA UPDATE

This newsletter is published quarterly and sent to all members of FRAXA Research Foundation. Permission is granted to reproduce and distribute this newsletter for noncommercial purposes.

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CONTRIBUTORS: David Busby

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Haruhiko Siomi, Ph.D.

Karel Svoboda, Ph.D.

DESIGN: Mary Lou Supple

PLEASE JOIN FRAXA

in supporting research
aimed at treatment
for fragile X



FRAXA is a national 501(c)(3) tax-exempt organization. You can join for a tax-deductible donation of \$25 or more per year. Every penny you donate goes to research: FRAXA has specific grants to cover all overhead. Members receive this quarterly newsletter and are welcome to participate as active volunteers.

Yes, I would like to join FRAXA

- | | |
|---|---|
| <input type="checkbox"/> Member (\$25+) | <input type="checkbox"/> Benefactor (\$500+) |
| <input type="checkbox"/> Donor (\$50+) | <input type="checkbox"/> Research Underwriter (\$1000+) |
| <input type="checkbox"/> Sponsor (\$100+) | <input type="checkbox"/> Named Research Fund (\$5000+) |
| <input type="checkbox"/> Named Research Chair (\$25,000+) | |



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FRAXA UPDATE

FALL 1999

VOLUME 6, NO. 3

A PUBLICATION OF
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FOUNDATION

"N EVER
D O U B T
that a small
group of
thoughtful,
committed
citizens can
change the
world.
I N D E E D ,
it's the only
thing that
ever has."

— Margaret Mead

Nobel Laureate James D. Watson Joins Scientific Advisory Committee

In 1953, Dr. James D. Watson and Dr. Francis Crick made the most famous scientific breakthrough of the 20th Century: the DNA Double Helix. They discovered that in each cell of our



Jeffrey Stevenson, James Watson, Bruce Stillman, Katie Clapp, Karel Svoboda, Esther Nimchinsky and Debbie Stevenson

bodies, our genes are arranged along two strands of DNA elegantly wrapped around each other in a double helix. This revolutionized medicine, and Dr. Watson, just 25 years old at the time, won the Nobel Prize for his work. So we are thrilled that Dr. Watson has agreed to help FRAXA reach for a breakthrough in fragile X research, and we are eagerly looking forward to working with Dr. Watson to bring fragile X research to the forefront of the scientific world in the 21st Century.

"I am most pleased to help FRAXA because I am highly impressed by the impact the organization has made in just a few short years. Though I have been trying to cut back on my public roles, my emotions do not let me and with the first big public payoff from the Human Genome Project being the 1991 cloning of FMR1, I want to see this great breakthrough appropriately used."

— Dr. James D. Watson, President, Cold Spring Harbor Laboratory, September 3, 1999

Also in this issue:

- Update on the Fragile X Breakthrough Act
- What are Top Scientists Saying?
- Fragile X Organizations Around the World

RESEARCH NEWS

NEW GRANT APPLICATIONS EXPECTED DECEMBER 1

FRAXA accepts new research proposals from scientists twice each year, with the next set expected on December 1st. After the proposals are evaluated by members of our Scientific Advisory Committee, the Board of Directors determines which proposals can be funded, based on quality and available funds.

Of course, "available funds" are donations from people like you. We thank you for all your

continued on page 7

FRAXA is a nonprofit, tax-exempt charity run by parents of children with fragile X syndrome. Fragile X syndrome is the most common inherited cause of mental retardation and developmental disabilities, affecting approximately 1 in 2000 males and 1 in 4000 females. FRAXA's goal is to accelerate research aimed at the treatment and cure of fragile X, by direct funding of promising research projects and by raising awareness of this disease.

Report from Washington

FRAGILE X RESEARCH BREAKTHROUGH ACT: UPDATE

by David Busby

Congratulations to all you KEY FRAXA people! All of your letters, phone calls and visits to members of Congress are bringing us a long way toward our goal: achieving fair funding for fragile X research.

CURRENT STATUS

Our main goal is to convince Congress to pass the **Fragile X Breakthrough Act of 1999**. This bill would fund at least three centers to conduct research aimed at the treatment and cure of Fragile X. Nearly every Member of Congress has received many calls, letters and visits from families, and as of November 3rd, 42 Congressmen and 14 Senators have signed on as Co-Sponsors of the bill (see box). We still have a long way to go, but you beginning to make Fragile X a household word in the House and Senate.

Our second goal has been to persuade Congress's Appropriations Committees to include Report language directing the NIH to accelerate and enhance fragile X research in its Fiscal Year 2000 appropriation. We are happy to report success: the Senate Appropriation Committee champions the Fragile X research cause, not just once but twice — in its directives to two of the National Institutes of Health! Its Annual Report urges the National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH) to increase research on Fragile X. (See text to the right.) The House Appropriation Committee report also includes language on Fragile X.

What does this report language mean? It is not as powerful as passing the Fragile X Breakthrough Act bill because a bill is permanent whereas these directives are operative only in fiscal year 2000. However, they do provide a much-needed head-start "ramp" for gearing up fragile X research.

WHAT YOU SHOULD DO RIGHT NOW:

By the time this newsletter reaches you, the 1999 Congressional session may be over. However, since the current 106th Congress will be in session through 2000, you have another year to get this bill passed. Keep up the pressure on your Members! If your representatives in Congress are not already cosponsors of the Fragile X Research Breakthrough Act (H.R. 1445 in the House and S. 1131 in the Senate), please call or write them again.



DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION AND RELATED AGENCIES APPROPRIATION BILL, 2000

Fragile X References in the Senate Appropriations Committee Report [Report 106-166] are as follows:

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT [page 139]

Fragile X – The Committee commends the NICHD for its research activities on Fragile X, the most common inherited cause of mental retardation. In its last two reports, the Committee has urged the NICHD to expand basic and applied research and testing of Fragile X. In 1998, the Committee recommended the convening of a colloquium of leading scientists to report on the most promising directions of future research and requested receipt of the recommendations emanating from the conference. The conference was held in December 1998. After due consideration of that report, the Committee urges the NICHD to implement the recommendations of the conference, especially the establishment of Centers for Fragile X research and long-term multi-center research collaborations. The Committee also urges NICHD to establish a loan repayment program for Fragile X research. The Committee urges that NICHD make funds available in fiscal year 2000 for this purpose.

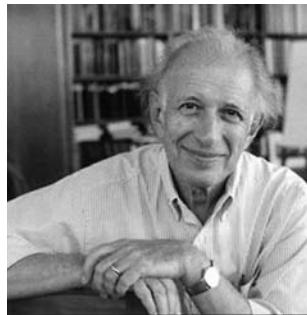
NATIONAL INSTITUTE OF MENTAL HEALTH
[page 164]

Fragile X – Fragile X is the most common inherited cause of mental retardation, first manifesting during childhood, but also affecting large numbers of adults. Fragile X is also the most common single-gene neuropsychiatric disease known, and as such is of vital interest to NIMH. Fragile X is potentially important as a research model for neuropsychiatric disorders such as schizophrenia, mood disorders, and autism. Individuals with fragile X constitute a remarkably homogeneous study population for advancing our understanding of these disorders.

Recent years have seen a convergence of research in psychiatry and molecular biology which are now beginning to help researchers understand the biological basis of human behavior and intelligence, as well as mental illness, on an increasingly more detailed level. Yet very few studies have utilized the most recent and advanced psychiatric research techniques to examine fragile X. The Committee urges the NIMH to promote increased awareness of this disorder among psychiatrists who treat adults with fragile X for the psychiatric manifestations of this disease. NIMH is also encouraged to promote rigorous scientific study of the currently available treatments commonly employed in fragile X patients, and to investigate promising new psychopharmacologic interventions.

WHAT ARE TOP SCIENTISTS SAYING ABOUT THE URGENT NEED TO FOCUS ON AND PRIORITIZE FRAGILE X RESEARCH?

"The ability to develop genetically modified mice has made it possible to relate single genes to actions of specific nerve cells in the brain on the one hand, and to long-term memory on the other. As a result, it is now possible to develop powerful new approaches to genetic disorders that affect memory, of which Fragile X is a prime example. We have every reason to believe that in the next decade we will gain a profound understanding of disorders resulting from the Fragile X mutation, and therefore we will be able to begin to develop effective new therapeutic approaches. It is likely that anything we learn about Fragile X will serve as a model for studying autism and help us to understand other disorders of memory like those associated with Down's syndrome and with Alzheimer's disease. . . ."



– **Eric R. Kandel**, M.D., University Professor, Columbia University, Center for Neurobiology & Behavior; Senior Investigator, Howard Hughes Medical Institute; and Lasker Prize Winner, -September 15, 1999

continued on page 6

MORE INFORMATION:

Details on H.R.1445 and S.1131 are available on the web at:

<http://www.fraxa.org>

Sample letters to your reps are here as well.

<http://thomas.loc.gov>

Search for "fragile X", and then click on "Bill Summary and Status" to see who has co-sponsored so far. This site also has names and addresses of all members of Congress.

You will find names and addresses of all members of Congress at: <http://clerkweb.house.gov/mbrcmtee/mbr-cmtee.htm>

Send a letter to any senator at: **Senator _____, Senate Office Bldg., Washington, DC 20510**

or to House members at: **The Honorable _____, House Office Building, Washington, DC 20515**

or call the Capitol, and ask for your senator or representative: **202-224-3121**.

Current list of Cosponsors as of November 4, 1999:

Senate

Bayh, Evan	Feinstein, Dianne	Hollings, Ernest F.	Landrieu, Mary L.
Boxer, Barbara	Hagel, Chuck	Kerrey, J. Robert	Lugar, Richard G.
Breaux, John B.	Helms, Jesse	Kerry, John F.	Reed, Jack
Edwards, John			Shelby, Richard C.

House of Representatives

Barrett, Bill	Kelly, Sue W.	Constance	Sherman, Brad
Bereuter, Doug	Kennedy, Patrick	Murtha, John	Slaughter, Louise
Blagojevich, Rod	Kingston, Jack	Neal, Richard	Smith, Christopher
Brown, Sherrod	LaFalce, John J.	Oberstar, James	Spratt, John M., Jr.
Cook, Merrill	LaHood, Ray	Olver, John .	Tauscher, Ellen
DeGette, Diana	Lowey, Nita M.	Pelosi, Nancy	Terry, Lee
Delahunt, William	Maloney, Carolyn	Price, David	Towns, Edolphus
Dreier, David	McIntosh, David	Quinn, Jack	Upton, Fred
Gilman, Benjamin	Mink, Patsy	Roukema, Marge	Watkins, Wes
Graham, Linsey	Moran, Jim	Schakowsky, Janice	Wise, Robert E., Jr.
Jenkins, William	Morella,	Sessions, Pete	Wynn, Albert Russell

With 20 FRAXA-funded teams at work in labs around the world, progress is being made. Here we report on a few exciting developments of the past few months.

Attempts to Reactivate the Fragile X Gene

GIOVANNI NERI, PH.D. ET. AL.

Catholic University, Rome, Italy

Giovanni Neri and his team at Catholic University in Rome, Italy, were funded by FRAXA in January 1999. This project is based on the fact that in almost all fragile X patients, the coding region of the fragile X gene (*FMR1*) is undamaged but is "turned" off by a defect in the region of DNA which regulates the gene. This defect causes methylation of the gene, a chemical change that neutralizes the gene so that it cannot produce its normal protein product. Dr. Neri's group is trying to find a way to reverse methylation and turn the gene back on.

In the November issue of Human Molecular Genetics, Chiurazzi et. al. report that using a combined approach of a demethylating drug and another drug that causes histone deacetylation, they see a marked degree of reactivation of the *FMR1* gene (see abstract below). While this is a very exciting result, it cannot be applied directly to humans brain cells because the specific drug used in this study is toxic and also only works in dividing cells. However, the study does show that the strategy of reactivating the gene is viable, something that, just a few years ago, many scientists thought would be impossible. The abstract of the article follows:

research

Synergistic effect of histone hyperacetylation and DNA demethylation in the reactivation of the *FMR1* gene.

Pietro Chiurazzi^{1,2}, M. Grazia Pomponi¹, Roberta Pietrobono¹, Cathy E. Bakker², *Giovanni Neri¹ and *Ben A. Oostra²

Université Cattolica, Rome, Italy, Erasmus University, Rotterdam, The Netherlands

ABSTRACT

Most fragile X syndrome patients have an expansion of a (CGG)_n sequence with more than 200 repeats (full mutation) in the *FMR1* gene, responsible for this condition. Hypermethylation of the expanded repeat and of the *FMR1* promoter is almost always present and apparently suppresses transcription, resulting in the absence of the *FMR1* protein. We recently showed that transcriptional reactivation of *FMR1* full mutations can be achieved by inducing DNA demethylation with 5-azadeoxycytidine. The level of histone acetylation is another important factor in regulating gene expression, therefore we treated lymphoblastoid cell lines of nonmosaic full mutation patients with three drugs capable of inducing histone hyperacetylation. We observed a consistent, although modest, reactivation of the *FMR1* gene with 4-phenylbutyrate, sodium butyrate and trichostatin A, as shown by RT-PCR. However, we report that combining these drugs with 5-azadC results in a 2- to 5-fold increase of *FMR1* mRNA levels obtained with 5-azadC alone, thus showing a marked synergistic effect of histone hyperacetylation and DNA demethylation in the reactivation of *FMR1* full mutations.



Dr. Flora Tassone (center) receiving the Isabelle Oberle Award from Dr. Jean-Louis Mandel (left). The conference chairman, Dr. Jean-Pierre Fryns, is at right.

Dr. Flora Tassone receives Isabelle Oberle Award

Dr. Flora Tassone, a FRAXA Fellow working in the laboratory of Dr. Paul Hagerman, University of Colorado School of Medicine, has received the Isabelle Oberle Award for the best scientific presentation on fragile X research by a young investigator. The award was presented by Dr. Jean-Louis Mandel at the International Conference on X-linked Mental Retardation and The Fragile X Syndrome in Strasbourg. The award was presented in honor of Dr. Isabelle Oberle, who worked on positional cloning of the fragile X gene in Dr. Mandel's laboratory from 1983 until her death at the age of 35 in November, 1991. Dr. Tassone's work has focused on the expression of the *FMR1* gene.

In particular, she has discovered that males with the premutation allele actually have higher levels of message than normal controls; in some cases, the levels are more than five times higher than normal. This observation changes the way we view the expression of the *FMR1* gene, and suggests new targets for increasing production of the protein product of the *FMR1* gene.

Advances in Understanding Neuron Connections

WILLIAM T. GREENOUGH, PH.D. ET. AL.

University of Illinois at Urbana-Champaign

A Press Conference and Symposium were held at the October 1999 Society for Neuroscience Annual Meeting in Miami, Florida, featuring advances in understanding the fragile X protein's role in neurons (brain cells). This article is based on a press release sent by the Society for Neuroscience to science writers across the country.

Dendritic Protein Synthesis: Implications for Synaptic Development and Plasticity

INTRODUCTION

Surprising insights into how neurons strengthen their connections may soon lead to new treatments for brain disorders such as epilepsy, Alzheimer's disease and fragile X. Neurons communicate with each other by passing information across specialized cell to cell contacts known as synapses. This vast communication network underlies our thoughts and emotions. For almost 30 years, researchers have known that a synapse's effectiveness and strength depends on the level of its use during development. In addition, more recent studies show that learning can modify and strengthen synapses throughout life.

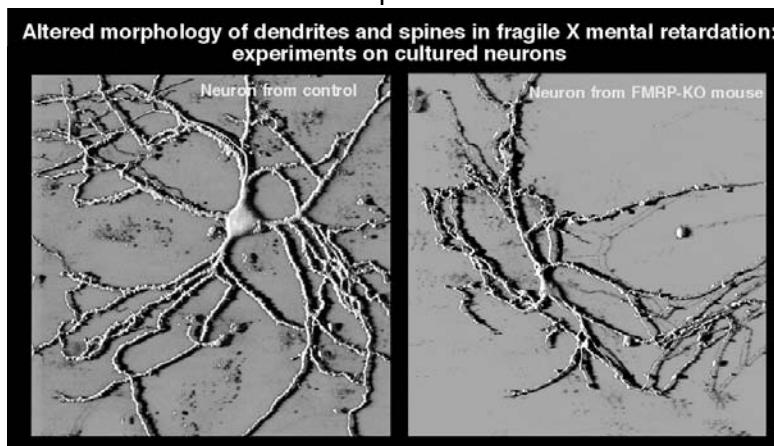
But what is the neuron's exact role? Scientists had no idea. Now an accumulating amount of research is finding that the branched endings that serve as the principal route of input to the neuron, or dendrites, can respond to the synapses to create proteins that may influence and strengthen connections. New studies identify the key players in this mechanism and also show what happens when there are errors. The findings may lead to new ways to boost the strength of connections to treat

diseases such as Alzheimer's disease or mental retardation where there is a lack of communication. It also may lead to new ways to limit the connections in diseases such as epilepsy where there is excess communication.

THE FRAGILE X PROTEIN IS NEEDED TO BUILD OTHER PROTEINS

William Greenough and his team of researchers have found evidence that the protein FMRP, which is missing in individuals with fragile X, plays an important role in the synapse strengthening process. The new studies show that, normally, FMRP is synthesized at synapses following synaptic activity and learning. The protein then participates in the synthesis of other proteins and, possibly in this way, plays a role in synapse maturation. "Our research shows that important aspects of the memory process as well as the cause of fragile X syndrome appear to involve synthesis of protein at the synapse," says Dr. Greenough. Earlier studies by Greenough found that animals boosted their synapse number and strength if they were exposed to opportunities for learning, or enriched environments. "We found that the synapses in

these animals were much more likely to be making protein than the synapses in animals housed in standard laboratory cages," says Greenough. To study this phenomenon more closely, the researchers developed a preparation of highly purified synapses called synaptoneuroosomes. They found that the brain chemical neurotransmitter glutamate caused the immediate local synthesis at the synapse of protein, including FMRP.



This shows two cells, one (left) from a normal mouse hippocampus and the other from hippocampus of a mouse which lacks the fragile X mental retardation protein (FMRP). Dendrites are the long arms branching off from the cell body, and the synapses are little bumps protruding from the dendrites which make connections with neighboring nerve cells. With FRAXA funding, Drs. Braun and Segal are comparing the number and shape of the spine synapses in fragile X mice with the synapses in normal mice. While it is too early in the study to draw conclusions, FMRP seems to be important for normal growth of nerve cells and their dendrites and synapses. Photograph courtesy of Anna Katharina Braun, Ph.D., Leibniz Institute for Neurobiology, Magdeburg, Germany

THE FRAGILE X PROTEIN HELPS DEVELOP CONNECTIONS BETWEEN NEURONS

The researchers analyzed FMRP's role by examining a mouse model of fragile X syndrome, which like humans cannot produce the protein. "We found that FMRP is necessary for the synthesis of other proteins that also are made at synapses," says Greenough. In addition, examinations of the brains of patients who died with fragile X syndrome and the mouse models found that they had more synapses than normal, but these synapses were not fully formed. "This may indicate that the synapses of

Continued on page 6

individuals with fragile X syndrome fail to go through the normal developmental process where some synapses take on a mature form and others are naturally eliminated,” says Greenough. “Together the research shows that FMRP is necessary for the synthesis of other proteins at synapses and possibly for the normal maturation of synapses and their roles in learning and memory.”

The research was supported by the National Institutes of Health and the FRAXA Research Foundation.

RELATED RESEARCH

At the Symposium, other investigators explained how nerve cell connections function and how errors in normal function cause diseases such as Alzheimer’s. Oswald Steward, Ph.D., discussed the mechanisms that tie synapse modification to the memory process, focusing on how messenger RNA moves to specific synapses. “There are increasing indications that problems with messenger RNA trafficking underlie certain disorders affecting the nervous system,” says Steward. Other researchers are uncovering the precise steps by which stimulation of certain synapses causes new protein to be made, which then in turn leads to changes in other synapses. “We think that understanding how synapses change is key to the inner workings of memory formation,” says Justin Fallon, Ph.D., of Brown University. “Once we further understand these workings, we will be able to determine if they are abnormal in diseases that affect memory, such as Alzheimer’s.” In the future, researchers might be able to repair or boost the system. “Possibly we might be able to develop specific drugs or genetic manipulation techniques that could aid in forming or retaining memories,” adds Fallon.

PRO BONO LEGAL REPRESENTATION

In case you wonder how FRAXA is able to afford legal representation, the answer is — it doesn’t. Dorsey & Whitney, a major U.S. law firm with 18 offices in this country and abroad provides legal representation pro bono publica. Since 1995, Dorsey & Whitney has devoted hundreds of hours to FRAXA. It has also made generous donations through the Dorsey & Whitney Foundation. David Busby, ex-partner and of-counsel to the firm in its Washington office (and a Fragile X parent), serves as general counsel. David Biegling serves as legislative counsel. Other members of the firm pitch in as necessary. Incidentally, Dorsey & Whitney is one of the national firms that has made a commitment to the American Bar Association to donate substantial pro bono time to worthy causes. FRAXA is indeed fortunate to be one of the beneficiaries of this commitment.

“The disease gene is cloned and identified, and it would be extremely desirable to develop a treatment for this disorder. I think such a treatment might be feasible, since the affected gene is present, but is turned off. If there were some way to activate this gene, this could be of great benefit to patients. I think this is a very worthwhile disorder for intensive research because of its frequency and because of the potential for prevention through genetic counseling and treatment of affected individuals.”

“. . . Although most of us in biomedical science have argued for strong general support for funding of the NIH as the major mechanism to achieve research advances, fragile X is a particularly significant and compelling disorder. . . .”

— **Dr. Arthur L. Beaudet, M.D.**, Professor and Chair, Department of Molecular and Human Genetics, Baylor College of Medicine, August 31, 1999

“At the present time, research is being largely supported by private monies, including that of the FRAXA Research Foundation. More government support is needed, and that is the purpose of the above bill. I know from past experience that NIH is reluctant to support research directed at specific diseases. Yet, much of the progress in at least two of the diseases I work with dystonia and Huntington’s disease, has come about from private sources urging federal support for the specific diseases. I anticipate similar benefits can be achieved for the Fragile X syndrome by the same means.”

— **Charles H. Markham, M.D.**, Professor Emeritus of Neurology, UCLA School of Medicine, June 30, 1999

“Fragile X research is on the leading edge in our understanding of gene-brain-behavior relationships; it serves as a model for many other neurodevelopmental disorders. Moreover, there is real cause for optimism in finding an effective treatment. With Fragile X, the coding portion of the gene is normal; it is just turned off, so no protein is produced from the gene. Thus, we do not need to introduce a new gene; we just need to find out how to turn on the silent gene that is already present. This breakthrough would lead to a cure.”

— **Randi Hagerman, M.D.**



Section Head of
Developmental and
Behavioral Pediatrics,
University of Colorado
School of Medicine, From
Dr. Hagerman’s testimony
submitted to the Subcom-
mittee on Health and
Environment of the House
Committee on Commerce on
Tuesday, October 12, 1999

support and hope that you will continue to contribute to FRAXA as often and generously as you can, so that we can accelerate research that will lead to a cure for Fragile X.

A key to funding the very best possible research is publicizing our grants. We have focused heavily on this task in recent months:

- We sent FRAXA grant and fellowship announcements to the Grants and Contracts Offices of major universities, and we registered on free and widely-used Internet-based grant resources such as GrantsNet
- We sponsored a booth at the October 1999 Annual Meeting of the Society for Neurosciences. This is the largest and most important meeting for neuroscientists, attracting about 25,000 researchers, including most of those currently funded by FRAXA. A full-page article on Fragile X research and FRAXA appeared in the October issue of the Neuroscience Newsletter, just in time for the annual meeting.
- We secured an agreement for joint funding of Fragile X research with the National Institute of Child Health and Human Development(NICHD). This joint funding program will be announced using the unparalleled publicity apparatus of the federal government. Stay tuned for more details, once the federal budget has been passed by Congress.

Andy Tranfaglia was featured in the Society for Neuroscience Newsletter, October 1999. Andy is 10 years old, has fragile X; his mom and dad are Katie Clapp and Mike Tranfaglia



RESEARCH NOTICES

PROJECT ON INFANT DEVELOPMENT

Dr. Don Bailey's group at Frank Porter Graham Child Development Center in Chapel Hill, NC, is studying the early development of infants with fragile X. Families with infants may wish to participate in this study. Children will be assessed every six months until age 2. All travel costs and a small stipend are covered. If you would like more information, please call Deborah Hatton or Jane Roberts at (800) 351-4603.

PROJECT ON ADOLESCENTS WITH FRAGILE X SYNDROME

Funded by the National Institutes of Health and the University of Wisconsin at Madison, this project has two goals:

1. To understand the nature of the problems in language and communication that affect many individuals who have fragile X; and
2. To learn more about the impact of having a son or daughter with fragile X on parents and other family members. I'm especially interested in providing more information to researchers, clinicians, and families about the issues and challenges that are unique to fragile X and that distinguish it from other conditions, such as Down syndrome.

We would like to include families that have a son or daughter with fragile X who is between the ages of 11 and 22. Participation requires one or two visits to the Waisman Center in Madison. We can cover limited travel expenses for families who must stay over night. Participating families will receive a report detailing their child's performance and will receive informational brochures and books. I can be contacted at: Len Abbeduto, Ph.D. Professor of Educational Psychology Waisman Center, University of Wisconsin, Madison

Madison, WI 53705, (608) 263-1737, e-mail:
abbeduto@waisman.wisc.edu.

TISSUE IS NEEDED TO ADVANCE RESEARCH

This is a difficult topic to raise, but researchers are in need of brain tissue in the event of the death of individuals who have fragile X. Much current work focuses on how fragile X brain cells differ from typical cells, and this work would advance more quickly if investigators could examine these cells. Brain banks do exist, but the typical way of preserving brain tissue for brain banks makes it less useful to researchers investigating fragile X. Therefore, special arrangements need to be made. Please consider calling Katie Clapp at FRAXA if you would like more information.

FRAXA KICKS OFF NEW WEB SITE: www.fraxa.org

Five years ago, www.fraxa.org was the only site we could find on the Internet devoted entirely to Fragile X. Now, fortunately, there are many sites offering valuable information on fragile X (see the following feature on Fragile X Organizations Around the World for a few examples), and the FRAXA site has been enhanced.

We are thrilled to announce that FRAXA's web site has been redesigned by Kevin Moffitt, an extremely talented webmaster at Putnam Investments. The new site has distinct easy-to-navigate sections: **What is Fragile X?**, **Research**, and **Getting Involved**. **What is Fragile X?** features clearly written explanations of the symptoms and cause of fragile X and how it is inherited. The

Research section includes application materials for investigators and descriptions of all the ongoing research projects. **Getting Involved** describes our chapters, events, and our major activities, such as advocacy for The Fragile X Breakthrough Act. The new site is a pleasure to browse . . . you will enjoy photos of our children and of many researchers.

We are very grateful to Kevin Moffitt for his fine work and elegant design of the site and for volunteering his considerable talents to FRAXA.

The screenshot shows the top navigation bar with links to Japanese, deutsche, español, français, and Hebrew. The main header "FRAXA" is on the left. To the right, a welcome message reads: "Welcome to the FRAXA Research Foundation Website. Our mission is to support research aimed at treatment for Fragile X syndrome." Below the message are three photographs: a smiling young boy labeled "About Fragile X", a young girl labeled "Getting Involved", and a researcher labeled "Research". On the left side, there is a vertical sidebar with three main sections: "About Fragile X" (with links to Symptoms, Cause, Inheritance, Prevalence, Testing, and Treatment), "Research" (with links to Research News, Grants & Fellowships, and Applications), and "Getting Involved" (with links to Member News, Join FRAXA, Donations, Chapter Info, Events, Advocacy, and Publications). At the bottom of the sidebar is a "QuickLinks" button.

MATERIALS AVAILABLE:

FROM NICHD:

National Institute of Child Health and Human Development has published a free brochure on fragile X syndrome. This 12-page brochure is useful for educators and medical professionals as well as families. Up to 50 copies of this brochure can be requested from the NICHD Clearinghouse, P.O. Box 3006 Rockville, MD 20847, (800) 370-2943 Fax: (301) 984-1473 , 8:30 a.m. - 5:00 p.m. eastern time, Mon. - Fri. Or, order online at the NICHD website: <http://www.nih.gov/nichd>

FROM FRAXA: FRAGILE X INFORMATION CARDS

HAVE YOU HEARD OF FRAGILE X?

Our loved one has Fragile X Syndrome

Fragile X is an inherited genetic disorder which affects 1 in 2000 boys and 1 in 4000 girls. It can cause:

- mental impairment ranging from learning problems to mental retardation
- behavioral challenges, like anxiety & hyperactivity
- autistic-like behaviors, such as

Many families have asked for a card that they can give to people who have no knowledge of fragile X. Business-size cards: \$10 per 100.

YOU CAN HELP

Please understand that new situations will cause our loved one to become anxious and afraid. Often, neither we nor (s)he can control this behavior. So please be encouraging and just *Smile!*

FOR MORE INFORMATION

FRAXA Research Foundation
45 Pleasant Street, Newburyport, MA 01950
web: <http://www.fraxa.org>

Fragile X Articles

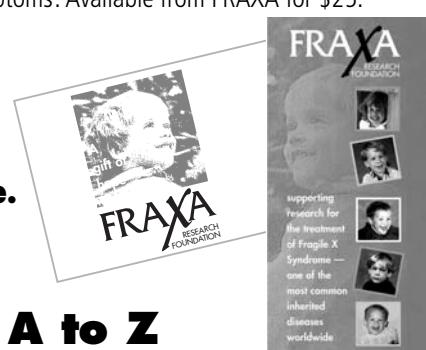
The Advocate 1995 – 1997, edited by Pamela Brode and published by Avanta Media Corp., 173 pages, \$25 postpaid within the U.S.

A Medication Guide for Fragile X

by Michael R. Tranfaglia MD, Psychiatrist
Medical Director of FRAXA

This guide is intended to help parents and others understand behavioral symptoms of fragile X and the medications commonly prescribed to help manage these symptoms. Available from FRAXA for \$25.

**Updated FRAXA
Brochures and
gift envelopes
are now available.**



Booklet available:

Fragile X : A to Z

Wendy Dillworth, FRAXA Michigan Chapter leader, has created a wonderful guide for families. *Fragile X - A to Z* is chock full of stories from daily life with fragile X children. Browse through helpful suggestions on topics such as adolescence, bike riding, computer software, and dental work. Wendy has collected these tips from the Fragile X Listserv with permission from each author. This 73-page soft cover guide is available from FRAXA for \$15 postpaid within the US; elsewhere please add \$5.

FRAGILE X ORGANIZATIONS AROUND THE WORLD

Fragile X families are organizing! Here is a partial list of groups in many countries.

ARGENTINA

Asociación Síndrome Fragile X of Argentina has a web site www.advance.com.ar/usuarios/omowen which includes descriptions in Spanish of many fragile X research projects being funded by FRAXA. You can email the association at omowen@infovia.com.ar or contact Jose Alberto García, parent, at **JAGARCIA@hipotecario.com.ar**

AUSTRALIA

Fragile X Association of Australia's web site is at www.ozemail.com.au/~fragilex/ and email is fragilex@ozemail.com.au; the contact is Graham Hook.

BRAZIL

La fundación Síndrome X Frágil de Brasil can be emailed at jveiga.klakim@uol.com.br

CANADA

Fragile X Research Foundation of Canada has a web site at www.fragile-x.ca/ Like FRAXA, this organization funds research and accepts new grant applications twice each year. Contact Carlo Paribello for more information at: 167 Queen Street West, Brampton, Ontario, Canada, L6Y 1M5. Phone: (905) 453-9366, email: FXRFC@ibm.net

GERMANY

The Interessengemeinschaft Fragile-X e.V. was founded in May 1993 by a group of parents. Today there are about 100 members. Their goals are to educate the public about Fragile X, to establish contacts between affected families and build regional groups, to achieve efficient support for affected children and adults, to exchange information with international parent groups, and to collect new scientific results and make them available.

Postadresse: 24576 Bad Bramstedt, Goethering 42

Telefon: 04192/4053, Fax: 07944/411

web site: <http://www.frax.de>, email: info@frax.de

IRELAND



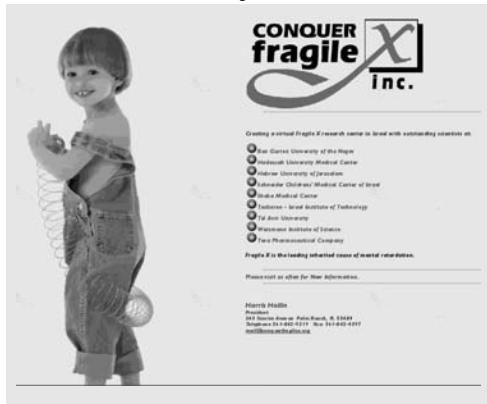
Dr. Mark O'Reilly, UCD; Alan Tate, Fragile X Society; Dr. Michael Tranfaglia, FRAXA; Deidre Carroll, NAMHI

professional awareness and encouraging research. The Society is a registered charity and has received a small number of grants to cover the costs associated with establishing the organization.

Activities: Under the chairmanship of Mrs. Mary Smith, the Society has focused on providing information and support to affected families and on increasing the awareness of the condition within the medical community

and the public at large. Two seminars have been organised. In August 1999, Dr. Mike Tranfaglia from FRAXA spoke on medications for Fragile X and on the latest research developments. During a hectic couple of days, Dr. Tranfaglia also addressed prominent Irish clinicians at a specially convened workshop and was interviewed on the leading national radio talk show.

Future Challenges: Family support, fund raising, membership expansion and the provision of materials to increase the awareness of Fragile X are all on the urgent 'To Do' list for 1999/2000. We also hope to create a Web site encompassing an 'Education Resource' for Fragile X. This initiative could well become a collaborative venture with other interested groups. Contact: Margaret Clarke, Phone: 01-458-2250, Email: mikilo@yahoo.com



ISRAEL

Conquer Fragile X, Inc. is a U.S.-based organization which funds fragile X research in Israel. Visit their web site at www.conquerfragilex.org or contact Harris Hollin, President, 245 Sunrise Ave., Palm Beach, FL 33480, phone: (561) 842-9219, Fax: (561) 842-0597, mail@conquerfragilex.org

ITALY

The Italian Fragile X Association has a web site at www.medicina.unige.it/ospiti/xfragile/

SPAIN

La Federación española de Asociaciones del Síndrome X-Frágil includes regional associations in many cities of Spain. Their web site is www.nova.es/xfragil/ and email is jgab@ctv.es

URUGUAY

Asociacion Síndrome X Fragil Uruguay's web site is www.xfragil.org.uy/ and email is xfragile@internet.com.uy.

Virginia Puntigliano writes: Just one year ago, my sister in law and I began to search the Web for information about this mysterious disease because her two sons had, at last, been diagnosed with fragile X. Some years before, her older son, Federico, began to show signs of being mentally impaired, but no doctor could give advice. In 1990, when Federico was seven years old, Joaquin was born. Nobody, neither doctors nor relatives, suspected that he was actually affected by the same syndrome his brother was. Stories like ours must sound pretty familiar to many people all over the world. When we began to search the Web, we had two purposes in mind. First: to know more about Fragile X, and second: to get in touch with other people with the same concern.

We wrote to FRAXA and Katie Clapp led us to Fernando Ayala in Spain. It was through him that we met with other parents and some professionals in our own country. And here we are. We are just about to obtain formal recognition of our Government.

Our Association is growing and we are working hard to raise public awareness and to help ensure that Fragile X Syndrome is diagnosed and properly treated. This is a gratifying experience that we want to share with everyone.

FRAXA EVENTS

FRAGILE X ALLIANCE OF OHIO'S THIRD ANNUAL GOLF TOURNAMENT

by Leslie Bagdasarian

The Third Annual Fragile X Golf Benefit was held on Monday, July 19 at Acacia Country Club in Lyndhurst, Ohio. Our aim was to raise awareness and research funds for Fragile X and we were very successful!

Over 260 people enjoyed the beautiful day of golf and evening attractions, including parents from the Fragile X Alliance, family members and friends who volunteered to run the event.

The golfing kicked off with a Shotgun Start at noon, with 152 golfers coming in from as far as New York, Wisconsin



Dr. Mike Tranfaglia presents Dr. Alan Tartakoff with a \$15,000 check from the Fragile X Alliance of Ohio FRAXA Chapter

and Texas. "Trick" holes using long and short clubs and a baseball bat were included along with numerous contests. All the trick holes were videotaped and replayed during the auction time for everyone to enjoy. Two hole-in-one prizes were offered – a \$10,000 cash prize and a new car – but unfortunately no one won! Following the golfing, our exciting Silent Auction included about two hundred items. A fun new event which ran at the same time was the "Gemstone Dig" in which gems, donated by IMG Jewelers,



The Fragile X Alliance of Ohio organizing team. Not pictured: Rick and Maryanne Haase

were planted in a large trough of sand and participants paid \$20 per scoop to sift for them. It looked like a gaming table in Las Vegas!

We were delighted to have Herb Score (former radio voice of Cleveland Indians baseball) and his wife, Nancy, return as the hosts of the evening and Live Auctioneers. The Scores also invited personal friends, Lou Groza, Dante Lavelli (former Cleveland Browns football stars and Hall-of-Famers) and their wives – it was an honor to have them with us! Our program included addresses by committee members and Nancy Score, a Hillary Rodham Clinton video (she spoke about Fragile X and encouraged those who are making efforts to increase research) and a CBS segment featuring the Clapp/ Tranfaglia family that were shown at the FRAXA Benefit in Washington, DC, this past April. Dr. Michael Tranfaglia

from FRAXA gave an update on the progress of Fragile X research and the political initiatives now in Congress. Our core committee of Leslie & Ara Bagdasarian, Maryanne & Rick Haase, Jill Maksoudian, Mike Sydenstricker, Rod Tyler and Jim Vitalie are to be commended for a job well done. Because of their hard work (along with the numerous volunteers), the Fragile X Alliance of Ohio is able to make a \$50,000 contribution to FRAXA Research Foundation. Part of this amount will go to renew the grant of Dr. Alan Tartakoff here at Case Western Reserve University in Cleveland.

If anyone would like a copy of our program from this event or have any questions, you can email Leslie at lbagdas@oh.verio.com.

FRAXA wishes to thank the entire Bagdasarian family for their ongoing commitment to FRAXA.

PATRICK'S PALS LUNCHEON AND LIVE CRAFT AUCTION

by Pamela & Jimmy Vershbow

Have you ever read Oh, the Places You'll Go! By Dr. Seuss? Well, when our son Patrick was diagnosed with fragile X syndrome at 10 months old, we couldn't begin to imagine what our lives would be like. As time progressed and the reality of the diagnosis set in, it started to become obvious that there were many places that we would not go. Many, many of the familiar places that "normal" parents take for granted we would never experience with Patrick . . . planning the simple children's birthday party, inviting his friends home to play,



buying him his first baseball uniform, and the list goes on.

The thing that was never clear is "Where would we go instead?" We never could



have imagined where this fragile life would take us. Last Sunday, October 17th, it took us to Woburn, to a hall filled with 200 of our closest friends and family; all of who were there to help us raise monies in order to find a cure for fragile X. It even took us to soliciting (for those of you who don't know me, this is a big step for someone who used to be too shy to greet a stranger). We 'worked the phones' and visited as many businesses as necessary in order to get everything donated so that we could "minimize expenses and maximize the help to those affected". Our phone never stopped ringing: "A

friend of a friend heard about the auction and is going to make a baby's hat and sweater set to donate".

"Wilson's Farm called me today, they are going to donate the entire Caesar Salad for the Luncheon!" This fragile life took us to a place where there are strong hearts and souls, where there are many generous people, to a place where there is hope.

By the time the Auction rolled around, we had

received over 80 handmade craft items, 17 door prizes, 3 raffle items and enough food to feed 200+ people! There were: hats, mittens & scarves, wreaths, mirrors, woodwork, bird

houses, afghans & quilts, and even a wall mural. The bidding wars were higher than expected and the spirit of giving was palpable in the hall! Our families had prepared the food and decorated the tables and hall with such love and perfection that we were asked over and over "Who did this? Is your family in the catering business?" The answer was no,

we are just in the caring business!

As Dr. Seuss said,

*I'm sorry to say so
but, sadly, it's true*

*That Bang-ups and Hang-ups
can happen to you.*

*You will come to a place
where the streets are not marked.*

*Some windows are lighted.
But mostly they're darked.*

*A place you could sprain
both your elbow and chin!*

*Do you dare to stay out?
Do you dare to go in?*

*How much can you lose?
How much can you win?"*

By the time the Auction ended, we had raised over \$12,000, increased awareness in our community, had a wonderful article written about us by the local newspaper AND added numerous new names to the list of "Patrick's Pals". Thank you all!

UPCOMING EVENTS:

The 3rd Annual Mary Higgins Clark Gala

will be held Sunday, April 30th at The Four Seasons Hotel in Chicago. For information, please call Jay Canel at 312-372-4142

On Thursday, March 2nd, Debbie and Jeffrey Stevenson will host a

Gala at The Russian Tea Room

in New York City. Please call Debbie at 212-828-1883 for tickets.

A Sports Celebrity Golf Tournament

will take place in Harrisburg, PA on June 14th, with an

Evening Banquet June 13.

Call Bill Parker at (717) 541-1500 for information.

We hope you can join us at these and other upcoming celebrations!

FRAXA POSTDOCTORAL FELLOWSHIPS REQUEST FOR GRANT APPLICATIONS

Upcoming Deadlines: December 1, 1999 and May 1, 2000

FRAXA offers fellowships and grants to encourage research aimed at finding a specific treatment and ultimate cure for fragile X syndrome:

- Postdoctoral fellowships of up to \$35,000 each per year
- Investigator-initiated grants for innovative pilot studies aimed at developing and characterizing new therapeutic approaches (no funding limit)

FRAXA is particularly interested in preclinical studies of potential pharmacological and genetic treatments for fragile X and studies aimed at understanding the function of the FMR1 gene. Applications are accepted twice each year. Information is available at www.fraxa.org or by contacting FRAXA.



*The Whitney and Vershbow families and their friends
at Patrick's Pals Luncheon and Live Craft Auction*

FRAXA UPDATE

This newsletter is published quarterly and sent to all supporters of FRAXA Research Foundation. Permission is granted to reproduce and distribute this newsletter for noncommercial purposes.

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PLEASE JOIN

FRAXA

**in supporting research
aimed at treatment
for fragile X**

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FRAXA is a national 501(c)(3) tax-exempt organization. You can join for a tax-deductible donation of \$25 or more per year. Every penny you donate goes to research: FRAXA has specific grants to cover all overhead. Members receive this quarterly newsletter and are welcome to participate as active volunteers.

Yes, I would like to join FRAXA

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