FRAXA Research Foundation Member Update

FALL 1998

VOLUME 5, NO. 3

New Fellowships and Grants Funded by FRAXA Research Foundation

As you know, FRAXA's primary purpose is to support research aimed at finding a specific, effective medical treatment for fragile X. Twice each year, in May and November, FRAXA accepts new applications from researchers all over the world. Five new projects have just been funded and are described here in detail. Thirteen projects are currently in progress. For an overview of all the work and how it fits together, please turn to Michael Tranfaglia's article on page 5.

Until now, FRAXA has primarily funded post-doctoral fellowships, which cover salary and benefits of young researchers who have recently earned their doctorates.

We now announce a new category of grants for principal investigators who want to pursue innovative new pilot studies aimed at treatment.

Please contact Katie Clapp at FRAXA for more information about these grants. Upcoming application deadlines are November 1, 1998 and May 1, 1999.

Inside this issue:

NEW AWARDS AS Of JULY 1998

(Note: Amounts are for first year)

1. Psychopharmacologic Studies in Fragile X Syndrome

RANDI HAGERMAN MD, Principal Investigator

KAREN RILEY MA Postdoctoral Fellow

The Children's Hospital, Denver, CO ($30,000)

There are few controlled studies of treatment of children and adults with fragile X syndrome. The FRAXA postdoctoral fellowship offers a unique opportunity to improve this situation. Dr. Karen Riley will act as a facilitator for collaborative research efforts with Drs. Loesch and Martin in Australia and with other centers in the US to improve and enhance treatment options for individuals and families affected by fragile X syndrome.

This project will focus on the primary and secondary benefits of pharmacological interventions. We will study the melatonin profile of children with fragile X syndrome and will carry out a controlled study of the efficacy of melatonin for sleep disturbances. Secondary benefits of improved sleep will also be explored and identified. These benefits could include decreases in outburst behavior, increased time on task, and

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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.

continued from page 1

improved social interactions. Sensory issues are also of paramount concern for individuals and families affected by Fragile X. Dr. Riley will evaluate the impact of stimulants, clonidine, and serotonin agents on the electrodermal (sweat) responses to visual, auditory, tactile, olfactory, and vestibular stimuli in collaboration with Dr. Lucy Miller, O.T.R.

The study will also involve the development and organization of neuropsychological protocols to be utilized for controlled studies of a variety of psychopharmacological interventions with children and adults with Fragile X. This team will strive to organize the participation of multiple centers, internationally and in the US, in the controlled trials of psychopharmacological interventions and in the exploration of secondary benefits. Drs. Riley and Hagerman report that they are eager to embark on this journey and are optimistic about the future findings.

2. Psychophysiological Measures of Arousal: Documentation of Treatment Effects & Impact of Disability

DONALD B. BAILEY, PH.D., MARIA L. BOCCIA, PH.D. Principal Investigators

JANE E. ROBERTS, PH.D. Postdoctoral Fellow

Frank Porter Graham Child Development Center, University of North Carolina at Chapel Hill ($30,000)

Clinical observations suggest that high levels of arousal (alertness) or the inability to normally modulate arousal affect many individuals with fragile X syndrome. In fact, many of the cognitive, social, and behavior problems associated with fragile X syndrome have been linked to high levels of arousal (hyperarousal). However, there has been virtually no experimental work evaluating and describing this phenomenon.

This project investigates the usefulness of heart activity data and cortisol levels as measures of arousal in boys with fragile X syndrome. Specific aims of this study are to: find the best method for documenting arousal; examine how arousal is related to behavioral and psychological functioning; quantify the relationship between protein production (FMRP) and arousal, and determine how physiological indices of arousal relate to selected classes of medications including sympatholytics and stimulants.

Information about the nature and impact of arousal in boys affected by fragile X syndrome has important implications for the assessment and treatment of these children. Because we know that behavioral and psychological functioning is negatively impacted by both high and low levels of arousal in individuals unaffected by fragile X syndrome, it is important to determine the role of arousal in individuals that are affected by fragile X syndrome. Hopefully, we will learn about the ways in which arousal affects boys with fragile X syndrome and how selected classes of medication are effective in regulating arousal.

research

3. Restoring FMRP Expression in Cells from Fragile X Patients

ANDRE HOOGEVEEN PHD, Principal Investigator

BEN OOSTRA, Co-investigator

Erasmus University, The Netherlands ($30,000)

Fragile X syndrome is caused by an unstable expansion of a CGG repeat in the 5' untranslated region of the FMR1 gene. The CGG repeat and the CpG island adjacent to FMR1 are hypermethylated and as a result the gene is silenced and no FMR1 gene product (FMRP) is produced.

Recently a number of normal males have been described with a full length CGG repeat expansion. In these males, the CpG island of the FMR1 gene is not hypermethylated and reduced-to-normal expression of the FMR1 protein was demonstrated. This indicates that there is a possibility of bypassing the hypermethylation seen in the fragile X syndrome transcription and translation is possile and sufficient in the presence of a repeat amplification.

Although we do not know whether the disorder (mental retardation) can be corrected, the most direct approach to treatment of fragile X syndrome is to restore the FMR1 gene product in neuronal cells of patients by demethylating the FMR1 promoter region.

Our studies will focus on the modulation of specific DNA methylation sites to remove or prevent methylation by using new antisense strategies in order to restore the FMRP expression. Standard DNA oligonucleotides already function effectively in many methods, including antisense strategies. However, the development of Peptide Nucleic Acids (PNAs) makes this strategy even more attractive. PNAs are a new class of DNA mimics in which the regular nucleobases are connected via a peptide-like backbone. PNAs are capable of recognizing sequences within duplex DNA by strand invasion; the effect on specific methylated sites has already been demonstrated.

We know that the timing of expression and the targeting to the brain will be a major problem to overcome. However, we think that because of its greater specificity in hybridization and its resistance to enzymatic digestion, the novel PNA clamping method might prove to be a promising approach to gene therapy in general and, in particular, for fragile X syndrome.

update:

4. Testing the potential of RNA for site specific demethylation

CHARLES LAIRD, PH.D. Principal Investigator
REINHARD STOGER, PH.D. Postdoctoral Fellow
University of Washington, Seattle ($15,000)

Dr. Stoger is exploring ways to safely and effectively demethylate (switch on) the FMR1 gene, in order to restore its normal function in individuals with fragile X syndrome (FRAXA Update, Spring 1998, p.6). In July, FRAXA awarded Dr. Stoger a six-month extension to his two-year fellowship. We are very pleased that Dr. Stoger has accepted a position at Guy's Hospital, London, starting in January 1999, leading his own research group, where he will continue his work on the fragile X gene.

5. Making available an improved strain of FMR1 knockout mouse

The Jackson Laboratory, Bar Harbor, ME ($10,000)

FRAXA has awarded funds to The Jackson Laboratory to make available to the research community a new-and-improved fragile X knockout mouse. Dr. Steve Warren at Emory University has graciously provided Jackson Lab with mice that he has recently developed: an FMR1 targeted mutant strain on a C57BL/6 genetic background.

The Jackson Lab Induced Mutant Resource makes important animal models of human diseases available for all interested researchers. Several years ago, FRAXA helped to arrange the importation of another strain (FVB) of fragile X knockout mouse developed by Dr. Ben Oostra and colleagues. It was since discovered that those mice had a gene mutation which causes blindness (retinal degeneration), which made it quite difficult to test the cognitive skills of the mice — they performed poorly in mazes, but it was probably because they could not see, not because of their fragile X mutation. The C57BL/6-FMR1 mice arrived at Jackson Lab in July and Jackson Lab has put a rush order on the importation process; if all goes well the mice should be available to the scientific community in November.

OTHER ONGOING GRANTS AND FELLOWSHIPS:

(Amounts are per year)

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

ROBERT BAUCHWITZ MD, PH.D. Principal Investigator
Columbia University, NY

CARL DOBKIN, PH.D., AND W. TED BROWN MD, PH.D. Co-Investigators, Institute for Basic Research, Staten Island, NY

Project Grant ($30,000)

7. Characterization of the Neuronal Function of FMRP

DAVID NELSON PH.D. Principal Investigator
Baylor University, Houston, TX
Postdoctoral Fellowship ($30,000)

8. Isolating and Characterizing the mRNAs that Bind FMRP

ROBERT DENMAN PH.D. Principal Investigator
Institute for Basic Research, Staten Island, NY
Postdoctoral Fellowship ($30,000)

9. Export of the Fragile X Gene Product

ALAN TARTAKOFF PH.D. Principal Investigator
Case Western Reserve University, Cleveland, OH
Postdoctoral Fellowship ($30,000)

10. Studies of the Fragile X Protein and Related Proteins

MARY KENNEDY PH.D. Principal Investigator
California Institute of Technology, Pasadena
Postdoctoral Fellowship ($34,000)

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

WILLIAM GREENOUGH PH.D. Principal Investigator
University of Illinois, Urbana-Champaign
Project Grant funded January 1998 ($150,000 for FY 1998)
Unrestricted Grant funded January 1997 ($50,000)

12. Mouse Models for Fragile X

BEN OOSTRA PH.D. Principal Investigator
Erasmus University, The Netherlands, Postdoctoral Fellowship funded July 1996 ($30,000), Renewed July 1997 ($30,000)

13. Studies of the Fragile X Knockout Mouse: Improving Memory Reversal Testing and Treatment with AMPAkines

W. TED BROWN MD, PH.D. Principal Investigator
Institute for Basic Research In Developmental Disabilities, Staten Island, NY
Postdoctoral Fellowship funded January 1997 ($25,000)
Renewed January 1998 ($37,000)

Report from Washington

BY MARY BETH BUSBY

Cordiality reigned at the meeting that Katie Clapp, David Busby and I had in July with Dr. Duane Alexander, the director of the National Institute for Child Health and Human Development (NICHD), and his colleagues, including Dr. Felix de la Cruz, head of the Mental Retardation Branch. They are very interested in fragile X research and in doing some creative things with FRAXA to attract new researchers. Stay tuned.

The big news is that the ***House Appropriations Committee Report***, released July 20, said:

> ***"Fragile X — Fragile X is the most common inherited cause of mental retardation and results from the failure of a single gene to produce a specific protein. The Committee urges NICHD to enhance its efforts to find a cure and expand the understanding of the role of the Fragile X protein in brain function. The Committee is pleased that NICHD has added Fragile X patients to its expanded program of autism research and urges the Institute to consider including Fragile X patients in the pediatric psycopharmacology clinical trials as an effort to develop safe and effective medication for individuals with Fragile X."***

Then the ***Senate Appropriations Committee Report*** was released with the following:

> ***"The Committee commends the NICHD for its continuing support for Fragile X research, and includes funds necessary for the Institute to further expand and strengthen its research activities on this disorder. Fragile X is the most common inherited cause of mental retardation. It is unique among developmental disorders because NICHD-funded research has identified the cause: the failure of a single gene to produce a specific protein.***
>
> ***"Although the protein can be produced synthetically, no cure or effective specific treatment has been found. The Committee urges the Institute to increase its efforts to find a cure for Fragile X, and to expand our understanding of the role of the Fragile X protein in brain function. The Committee is pleased that the NICHD is co-sponsoring with the FRAXA Foundation an international Fragile X conference in December 1998. The Committee looks forward to receiving a report on the recommendations and goals set at the conference. An important portion of the conference will address increased research efforts to develop effective treatments for individuals with Fragile X, including testing of existing medications and development of new psychopharmacologic medications that are safe and effective. The Committee is pleased that NICHD has added Fragile X patients to its expanded program of autism research, and urges the Institute to include Fragile X patients in the pediatric psychopharmacology clinical trials being conducted by autism investigators as another effort to develop safe and effective medications for individuals with Fragile X."***

The Sixth International Fragile X Conference, sponsored by the National Fragile X Foundation in Asheville, North Carolina, was a solid three days of highlights. FRAXA was proud to have provided a $2000 grant to enable several researchers to travel to this conference. A major thrill was the banquet at which FRAXA-funded William Greenough received the National Foundation's William T. Rosen Research Award for outstanding research achievements in the field of fragile X. Dr. Greenough says that he keeps the award on the desk of his colleague, Ivan Jeanne Weiler, Ph.D, since it is as much in tribute to her for her work as to him for his. We are delighted for Dr. Greenough. Also honored at the banquet were FRAXA's Katie Clapp and Mike Tranfaglia (are those names familiar?), who received the Halstead-Bresnahan Family Award "in recognition of an outstanding contribution by a parent to the fragile X community." I went up to Katie and Mike afterwards and said, "Richly deserved, my friends." And how!

Also at the conference in Asheville, we discussed the importance of letters to Congress in John Harrigan's legislative session. There was lots of energy in the room, and we hope the enthusiasm generated there will energize all parents. As we've said before and will say again (and again), members of the Congress really do respond to letters from people like you who may or may not vote for them. We "Washington-types" can only point the way. We can't vote for your representatives — and they know it!

From Asheville, David and I drove to Greenwood, South Carolina, where we were delighted to speak — along with fellow FRAXA parents Paul and Sandy Shewmaker and their son Daniel — at a fragile X conference at the Self Research Institute of Human Genetics, the "Mayo clinic of genetics." Drs. Herb Lubs, Grant Sutherland, and Francois Rousseau were the eminent researchers who spoke, as well as Dr. Roger Stevenson, who coordinated the conference. David and I were — as always — blown away with their brilliance and the depth not only of their commitment to our children, but also that of the young researchers who were present. One of these days, folks. Just you wait. Of course, "waiting" is what's so hard to do when our children's development is involved.

While we wait for the breakthrough, we're ever mindful of the many dollars it takes to fund the research; so we're whiling away the end of summer by making plans for the second Mary Higgins Clark gala, which will be in Washington on April 19, 1999, at the Four Seasons Hotel. I hope those of you who think you might be able to come will put it on your calendars now; and please let us know so that we can be sure you'll receive an invitation. We are — needless to say — so grateful to both Mrs. Clark and her daughter, Carol (and of course to our wonderful board member, Mary Jane Clark, who did a marvelous job as chair of this past spring's gala in New York) for agreeing to participate in this event. Diane Rehm, Washington's premier radio talk show host, has agreed to co-chair the gala with me; and the master of ceremonies will be Roger Mudd, Washington commentator, analyst, historian, and educator.
So ya'll come, okay?

Fragile X Syndrome: Overview of New Research

by Michael R. Tranfaglia MD, Medical Director, FRAXA Research Foundation

Introduction

The gene for fragile X syndrome was only relatively recently discovered, yet research in the past five years has taught us an enormous amount about the basic biology of fragile X. We now know a great deal about the cellular function of the fragile X protein, FMRP, and this knowledge can be expected to result in improved treatments over the next few years. In addition, the insights we are gaining into the biochemical lesion in fragile X are helping scientists to understand other forms of mental retardation and autism spectrum disorders.

Cell Biology

An understanding of the basic functions of a cell is necessary for any discussion of the role of the fragile X gene in the workings of the central nervous system. As is well known by now, fragile X syndrome is caused by a trinucleotide repeat sequence which is abnormally expanded and which disrupts the proper function of the gene. This long stretch of CGGs is located in an untranslated promoter region of the gene, so FMR1 (the fragile X gene) itself is normal in the vast majority of cases. However, our cells are very sensitive to the presence of abnormal genetic material, and so shut this gene down through a chemical process called methylation. Several research projects currently under way aim to reactivate FMR1 by reversing this process of methylation; FRAXA-sponsored research at the University of Washington (Dr. Charles Laird and Dr. Reinhart Stoger) has mapped out all of the sites on the gene where methylation occurs, and we have just funded a new project which will utilize a recently developed technique for targeted demethylation (Dr. Andre Hoogeveen).

When everything is working properly in a cell, DNA is transcribed into messenger RNA. DNA, which makes up most of our chromosomes, resides exclusively in the nucleus of the cell. This is a relatively inaccessible location, a kind of miniature vault where the master copy of the genetic code is protected; DNA never leaves the nucleus, but instead the messenger RNA is used as a working blueprint to carry information to the rest of the cell. The process by which messenger RNA is shuttled to the outlying areas of the cell is still relatively poorly understood, but one of the active sites on the fragile X protein is indicative of just such a shuttling function. Dr. Alan Tartakoff is investigating the mechanism by which the fragile X gene product is exported from the nucleus.

Once the messenger RNA is taken to the appropriate place in the cell, it can be translated into protein; however, this process is tightly regulated. One of the most significant breakthroughs in understanding fragile X has been the discovery that FMR protein is translated at the site of synaptic (neurochemical) activity. Since the way a protein's translation is regulated is usually related to its cellular function, this was a major clue for fragile X researchers. Dr. William Greenough first discovered this at the University of Illinois, and since this discovery his lab has become a major site for FRAXA-funded research.

Neurobiology

Neurons are unique cells in that their function is highly influenced by their shape. Neurons receive input from other cells in the brain through numerous contacts called synapses; each cell acts as a tiny computer by summing up all the inputs into it and producing an output signal. Inputs from other cells are received on dendrites, and output is sent through the axon. Translation of FMR protein has been localized to the dendrites, and it now appears that the more active the synapse, the more FMR protein is produced. Subsequent research has shown that this protein also facilitates the translation of numerous other messenger RNAs. With FRAXA funding, Dr. Robert Denman in Staten Island is currently cataloging all of the messenger RNAs which interact with the fragile X protein, and this line of research may produce numerous candidate genes for other developmental disabilities.

What do all these proteins do in the dendrites? It appears that synapses change shape as they are used more frequently; more active synapses become more efficient and stronger connections. At first, it was thought that this happened by simple enlargement of the contact area; but recent research has shown that the process is more elegant than this. Most synapses, particularly those in areas of the brain involved in learning and memory, occur on tiny processes of dendrites called dendritic spines. In immature animals, including humans, these spines are long and slender; research has shown that synapses on these immature spines form relatively weak contacts. As synapses receive more input, these spines actually become shorter and stouter, resulting in a much stronger contact. Examination of brains from humans with fragile X shows that these dendritic spines are long, slender, and immature in form. This implies that the fragile X protein is critical for producing and regulating the dendritic response to synaptic activity.

Interestingly, two other genes have been discovered which are similar in their genetic sequence to FMR1; dubbed FXR1 and FXR2, the protein products of these genes appear to work together with the fragile X protein in the dendrites. There has even been some research which suggests that these other proteins may compensate for the absence of the fragile X protein. It is possible that many cases of developmental disorders in which fragile X testing is negative may be explained by abnormalities in these genes. Dr. David Nelson's team at Baylor University and Dr. Mary Kennedy's team at California Institute of Technology are studying the interactions between the FMR protein and other proteins that may be involved in fragile X syndrome.

Animal Models

Much of the research described above depends to some extent on testing in rodents. The original animal model for fragile X syndrome, the FMR1 knockout mouse, was developed by Dr. Ben Oostra and colleagues by breeding mice that lack the normal fragile X gene. FRAXA is currently funding development of improved mouse models in the lab of Dr. Ben Oostra and helping to make fragile X mice available to all interested scientists through funding for Jackson Laboratory, a facility which specializes in providing animal models to the research community. FRAXA is also funding behavioral testing of the fragile X mice (Dr. Ted Brown).

Treatment Implications

So, it is likely that fragile X protein is responsible for coordinating a large suite of genes which remodel synapses and strengthen contacts between neurons in a use-it-or-lose-it fashion. This protein regulates translation of many other proteins and shuttles required messenger RNA to active areas of the dendritic arbor. This knowledge has already helped us to understand why individuals with fragile X syndrome are affected in the ways that they are, and it should lead to enhanced treatment. Our current focus is identifying ways to replace or compensate for the lack of FMR protein; ongoing research includes a gene therapy trial (Dr. Robert Bauchwitz) and pilot studies of promising pharmaceutical agents (Dr. Randi Hagerman, Dr. Don Bailey).

FRAXA GROWS . . .

A Note from the Editor:

This has been an eventful summer for FRAXA: 5 new grants were funded, Congress has spoken out supporting increased research on fragile X, we have participated in the Sixth International Fragile X Conference, we've moved into a real office, and the list goes on. To report on everything in a timely fashion, we've chosen to expand this Fall issue of the FRAXA Update. The next full issue of the newsletter will reach you after the first of the year, when another round of fellowship/grant funding will be complete. Later in the fall, we will send an update report on projects in the works. Please make a note of our new address. Thank you for all your support!

-Katie Clapp, President

Dr. Owen Rennert

Dr. Rennert will be working with Dr. Felix de la Cruz and others at NICHD; one of his main roles will be to identify priority areas for research funding. Since NICHD is the primary federal agency responsible for fragile X research, it would be a conflict of interest for Dr. Rennert to continue his advisory role with FRAXA. Dr. Rennert writes "I remain committed to the wonderful objectives and goals all of you have worked towards." We are deeply grateful to Dr. Rennert for his all of his invaluable guidance over the years and congratulate him on his new position.

FRAXA ORGANIZATIONAL NOTES

by Katie Clapp

Many of you know that FRAXA started in 1994 as just a handful of parents operating out of the back rooms of their houses. As FRAXA's fifth year draws to a close, I have some changes to report with both qualms and excitement:

- FRAXA is no longer a 100% volunteer organization.
- FRAXA now occupies a real office, rather than a Post Office Box. Please make a note of our new address: 45 Pleasant St., Newburyport, MA 01950. Phone and fax remain the same.
- We bid a fond fairwell to our Chief Scientific Advisor, Dr. Owen Rennert, and welcome a new volunteer, Leslie Eddie.

FRAXA has grown beyond the wildest dreams of most of us who have been involved since the early days. Each year contributions and research funding have more than doubled, until this year, during which we expect FRAXA research grants and fellowships to top half a million dollars. We are doing all we can to sustain this pace of growth for a simple reason: that is what will lead most quickly to a cure for fragile X.

Administration of the Foundation has been a full-time job for several years now, and it is certain to continue to expand. I have recently accepted a (modestly) salaried position as FRAXA's President/Executive Director. In spite of this change, we still aim to keep our administrative overhead costs as low as is humanly possible in order to fund as much research as we can.

As we move to the new office, we welcome Leslie Eddy, who is volunteering one day a week to FRAXA. Leslie has seven years experience in sales, currently works for Family PC magazine, and has extraordinary energy and dedication. Her two-year-old daughter Allison has fragile X. Welcome aboard, Leslie!

Finally, in August Owen Rennert, MD, stepped down as Chair of Pediatrics at Georgetown and assumed the position of Special Assistant to the Director of NICHD, assigned to the Center for Research for Mothers and Children.

AAP NEWS

"Not an easy diagnosis to make"

50% of fragile X patients lack telltale signs

Educating Doctors

Fragile X Syndrome was featured on the front page of the June issue of AAP News, the official newsmagazine of the American Academy of Pediatrics. This 3-page article explains when a doctor should test for fragile X, how a gene mutation leads to the syndrome, and suggests ways caregivers can help affected families. Best-selling author Mary Higgins Clark contributed a sidebar about her grandson, David, who has fragile X. Reprints of this article are available from FRAXA in print or electronic (Acrobat) format.

Supporting FRAXA via the United Way

Contributions to FRAXA through the United Way have been growing steadily. Although FRAXA is not a United Way member organization (because the paperwork is a jungle), people can designate that their United Way contributions go entirely to FRAXA by listing our name and Tax ID (04-3222167) on the forms provided by employers. We have recently received contributions from the following United Way chapters:

United Way of the National Capital Area (Washington DC)
United Way of Massachusetts Bay
United Way of Southwestern Pennsylvania
United Way of South Hampton Roads (Virginia)
United Way of Orange County (California)
Long Island's United Way
United Way of Southeastern Connecticut
United Way - Cleveland Ohio

We are also receiving contributions through America's Charities, Inc. Thank you to all of you who are contributing in this way! One particularly helpful aspect of these contributions is that they come regularly over the long term so we can count on them when we commit to funding new research grants.

Thank You Philadelphia!

Cristy and Mitch Hollin, Chairs of the evening

Irv Govberg and Harris Hollin enjoying the evening

Robin Batoff chatting with guests

The Triple Threat Theatre Company performed for the group

by Cristy Hollin

Forget soft pretzels, cheesesteaks and Rocky. Philly should really be known for its charitable inhabitants, who are the real reasons why it is known as the City of Brotherly Love.

This generosity showed at the first annual Philadelphia FRAXA fundraiser chaired by Cristy and Mitchell Hollin and co-chaired by Sylvia and Billy Bell and Sande and Harris Hollin. Over 275 people sipped cocktails, nibbled hors d'oevres, and joined in a raffle and silent auction. Katie Clapp and Brenda Finucane, MS helped educate the crowd about fragile X and FRAXA. Then a very vivid video "A Mother's Perspective," was shown. Finally, all were entertained by the Triple Threat Theatre Company and Melissa Stevenson. It was a night of hugs, love, laughs and tears, and when it was over, Philadelphians had contributed over $100,000 to FRAXA!

We express our gratitude to the following people, whose signficant contributions are already helping to advance research on fragile X: Abramson Family Foundation, Alter Foundation, Scott and Karen Tarte, Stephen and Helene Kendall, Jewish Community Foundation, Marc and Suzanne Bell, William and Sylvia Bell, Lorre and Anthony Brenner, Arthur and Nancy Broll,Patricia Cloherty, Raymond and Ellen Goldberg Foundation, Jerome and Maxine Goodman, Jeffrey and Amy Harrow, Harris and Sande Hollin, Marjorie and Lewis Katz, Lamm Family Foundation, Scott and Cynthia Marshall, Gary and Karen Neems, David M. and Lorraine Popowich, Mitch Scherzer, The Howard and Debbie Schiller Foundation, Joseph Shanis, Janet Effland and William Urbach, Abby and Jon Winkelried, Nancy and Richard Wolfson Charitable Fdtn.,George Zallie,

A very special thanks goes out to the following for underwriting portions of the event:

Ellen and Ray Goldberg, Diane and Arthur Raynes, Korman Suites, World Class Parking, Firefly Books Ltd., Mellon Private Asset Management, Peter Scott Ruben Orchestras, Ed Leskin Photography

We also thank the suppliers of goods and services for our raffle and auction, including (but not limited to):

Travel One, Govberg Jewelers, Dan Brody Photography, Four Seasons Hotel, Boyds of Philadelphia, Saks Fifth Avenue, Neiman Marcus, Rittenhouse Hotel, The Palm, The Saloon, and many, many others. Finally, thank you to each and every member of our committee: we could not have done it without you. Of course, Cristy is already planning the Second Annual Philadelphia FRAXA fundraiser; we hope to see you all there!

Another incredible fundraising cocktail party was held at the Rittenhouse Square home of Sande and Harris Hollin Sunday May 17th. More than $25,000 was raised for FRAXA Research. Guests were enthralled by singer Peggy King. They also viewed a video prepared by Cristy Hollin on Matthew, her son and the grandson of Sande and Harris. Many of the guests were introduced to Fragile X for the first time.

Gerald Gushner, Ray Goldberg and Morton Weinstock

Harris Hollin and Sylvia Bell, Vice Co-Chairs and grandparents of Matthew

Singer Peggy King; Sande Hollin and friends looking on

Mitch Hollin

FRAXA *Chapters*

Wendy Dillworth and Kathy May have agreed to serve as joint Chapter Coordinators for FRAXA. Please feel free to call either Wendy or Kathy to explore ideas for growing your chapter or starting a new one. Or, call Katie Clapp at FRAXA Headquarters to request extra copies of the newsletter or brochure or other materials.

Wendy Dillworth
P.O. Box 24
Richland, MI 49083-0024
Phone: (616) 629-5890

Kathy May
11421 Pope's Head Rd.
Fairfax, VA 22030
phone: (703) 278-9144
E-mail: Kmay@erols.com

MASS/HEADQUARTERS

Katie Clapp
Headquarters has a new address:
45 Pleasant St.
Newburyport, MA 01950
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Fax: (978) 463-9985
E-mail: info@fraxa.org
http://www.fraxa.org

In May, Dr. Mike Tranfaglia traveled to the Waisman Center in Madison, Wisconsin, to talk about fragile X research and treatment from a parent perspective; the question and answer session that followed ran for hours. He also greatly enjoyed the opportunity to meet with members of FRAXA's Chicago Chapter at the home of Jody Goldsmith and Avis Primack. Elizabeth Berry-Kravis, MD, Ph.D., attended this meeting, and there was much discussion of ways to reinvigorate her Chicago fragile X clinic and fund clinical trials of treatments for individuals with fragile X.

On Sunday, June 7th, Patrick's Pals II 3-on-3 Basketball tournament took place in Cambridge at the Shady Hill School. This year's event raised over $14,000! Pamela and James Vershbow write: "Contributions were received both from people who participated in the tournament and from just as many people who could not come that day. Over the past two years, this event has shown us how many truly wonderful, caring people there are out there, and to all of them, there isn't a way to show enough gratitude. The ultimate winners, of course, are the children with fragile X and the devoted people who work so hard on behalf of FRAXA's efforts to find a cure. The Whitneys and the Vershbows held their 5th Annual Huge Yard Sale to benefit Fragile X on a Saturday in May. Once again it was a great success ... albeit a wet one! In the middle of a seven-day rain storm, somehow we were blessed with nothing worse than spurts of drizzle. Rain doesn't seem to keep the serious yard sale shopper away though; by day's end we had raised $4,100. Nor did rain scare off our dedicated volunteers who started setting up at 4 a.m. this year! Thanks to all of you!

Patrick gives a high five

The winning teams

Patrick Vershbow at the 5th Annual Whitney/Vershbow Yard Sale

The Whitney/Vershbow team has decided to shift gears next year so look out for news of a "Patrick's Pals Auction/ Luncheon to Benefit Fragile X." Rest assured that Yard Sale VI will be back in the Spring of 2000!

NEW CALIFORNIA CHAPTER

Jane Jones has moved to
1951 Rodeo Drive
Imperial, CA 92251
Jane Jones
P.O. Box 189
Duncan, AZ 85534
email:
jjajones@aepnet.com
phone: (520) 359-2506

CALIFORNIA SOUTHERN AFFILIATE

Fragile X Assoc. of So. California
PO Box 6924
Burbank, CA 91510-6924
Phone- 818 754-4227
Contact: Sali Farber or
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GEORGIA

Lee Anne Muma
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In July, the Muma Family held a bowling tournament to benefit FRAXA. Lee Anne Muma writes:

"The day was an amazing success. The weather was a gift from heaven – 84 degrees, no humidity, clear, sunny skies. The kindness of friends, family, and even strangers is overwhelming; pledges are still coming in, but so far total over $4400! We finished finished the day at my parents' place with a huge cook-out, doo rprizes and lots of fun!"

HAWAII

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CHICAGO

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The Chicago chapter's June bowling/pizza/auction/raffle was spectacular. Jody Goldsmith writes: We had the best fundraiser, not to mention bringing in over $3,300 dollars! Avis Primack and I were so very proud watching everyone participate. Gela Majesky outdid herself organizing, transporting, running, and waking up at 6 AM to get the balloons filled with helium — nothing was too hard for her! Over 100 people showed up that day. 20 bowling lanes were designated for FRAXA as well as a private room. You should have seen how beautifully the auction room was decorated. Karen Dorfmeyer, Bev Romanoff and Sarah Urycki romanced the room with tulle and flower swirled table cloths, jewelry displayed on black velvet, and a lolli-pop game overflowing with bright colored prizes for the winners, while ten tables glimmered with huge baskets of goodies wrapped in opalescent celephane by Linda Canel.

A great time was had by all, but the best part was watching the smiling faces of our children. For many it was the first time they had been to a bowling alley. Not only did they learn how to bowl, but each child, verbal or nonverbal, showed us all how to have a great day. One of funniest moments in the afternoon was when Bev's son Adam, who has fragile X, sat up high on a swivel chair overlooking the lanes and said "Welcome to my office."

Gela Majesky and Maureen Schmidgall

INDIANA

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Dave and Mike Schmidt with Beanie Babies

Gail Harris-Schmidt organized a "Liberty Bear" Beanie Baby sale. Beanie Baby fervor reached new heights when a $5 bear sold for $200 to benefit FRAXA!

Paula and Matthew Clift

Paula and Patrick Clift of Batesville, Indiana, discovered just last fall that their son Matthew is affected with fragile X. In May they held a bowl-a-thon for FRAXA, raising over $2300 and still counting. Paula writes "we came up with a list of people we knew well – friends, coworkers, family – and sent everyone a letter describing fragile X and asking that they participate or donate . . . My husband and I also took a vacation day and went around to a lot of the local businesses and asked for door prizes. We came out with about 80! . . . There are too many people to thank in this letter – we were overwhelmed by the support we had from all!"

KENTUCKY

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OHIO – GREATER CINCINNATI

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OHIO – GREATER CLEVELAND/AKRON

The members of this chapter surprised everyone, including themselves, by raising over $55,000 at their second annual Golf tournament. Although most golf courses feature 18 holes, the Cleveland Chapter attracted corporate 41 hole sponsors, and, we are happy to report, every sponsor was happy to share the limited resources. The auction alone brought in $20,000, thanks especially to Rick Haas who found some wonderful prizes, such as the right to throw the first pitch at a Cleveland Indians game, which went for $3100!

The Cleveland Chapter has decided to designate part of the Golf Tournament proceeds to fund fragile X research under Dr. Alan Tartakoff at Case Western Reserve University. As you may know, FRAXA has awarded funds to Dr. Tartakoff for his studies of the fragile X gene product, and we are thrilled that the Cleveland Chapter is able to cover a large part of this award.

OREGON

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SOUTH CAROLINA

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This group holds regular meetings; call Paul or Sandy for details.

VIRGINIA/CAPITOL AREA

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TEXAS

Roger Hoh
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The Meadows Foundation of Texas has generously awarded FRAXA a grant of $25,000 to help fund ongoing research in the laboratory of Dr. David Nelson at Baylor College of Medicine in Houston. The Meadows Foundation was founded by Algur H. and Virginia Meadows to help people and institutions of Texas improve the quality and circumstances of life for themselves and future generations. It is now one of the top 100 foundations in the U.S. in terms of total giving. Visit The Meadows Foundation web site at http://www.mfi.org.

Over the first half of 1998, Randalls Supermarket FRAXA shoppers, in Houston and Austin, and Tom Thumb Supermarket FRAXA shoppers in Dallas purchased over $40,000 in groceries. As a result, these stores are donating over $400 to FRAXA to support fragile X research by Dr. David Nelson's team at Baylor College of Medicine, Texas.

Our goal is to purchase $100,000 in groceries by the end of 1998. The Randalls/Tom Thumb donation would be $1000. If you live in Houston, Austin, or Dallas, please link your purchases with the 3715 FRAXA number.

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FRAXA Research Foundation

CYBERSPACE

What is The 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.

How to join

Send mail to LISTSERV@LISTSERV.CC.EMORY.EDU with the following command in the body of your e-mail message:

subscribe fragilex-l (that's "L" for "List")

An *extremely* useful option: the digest

If your life is full enough without a dozen or so additional email messages each day, the digest option bundles all your listserv messages and delivers them in one daily email:

set fragilex-l digest (that's "L" for "List")

How to leave (unsubscribe)

You can join and leave the group as many times as you like. It is important to sign off before you go on vacation so piles of unread email don't flood your inbox! To sign off, send mail to LISTSERV@LISTSERV.CC.EMORY.EDU with the following command in the body of your e-mail message:

signoff fragilex-l ("L" for "List" again)

Suzzane Anderson, Northern Florida FRAXA Chapter head (E-mail: SSKM@aol.com) runs an AOL chat every week. See Florida South for details.

AVAILABLE FROM FRAXA:

A Medication Guide for Fragile X Syndrome

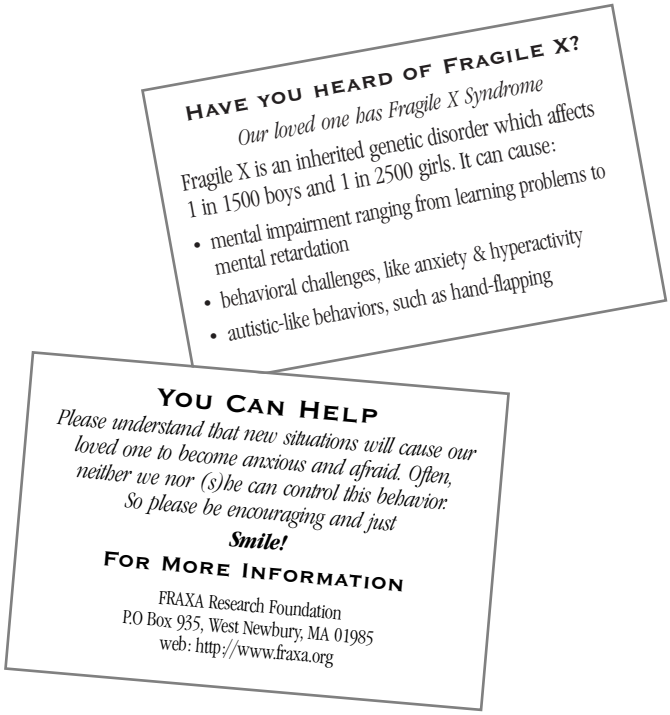
by Michael R. Tranfaglia MD, Psychiatrist
Medical Director of FRAXA

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.

FRAGILE X INFORMATION CARDS

FRAXA sells fragile X information cards.

These are business-size cards that 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.



New 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).

Do You Want to Know a Secret?

Dan Rather, anchorman for the CBS Evening News put it candidly: "The secret is out: Mary Jane Clark is one of the most exciting novelists in America today."

A media thriller by a network news insider, **Do You Want to Know a Secret?** (St. Martin's Press: November 1998; $23.95; hardcover) marks the debut of talented newcomer Mary Jane Clark. Like Eliza Blake, a character from the novel who is an appealing and talented newswoman on the rise, Mary Jane's stock as a writer of page-turning novels will soon rise with the release of **Do You Want to Know a Secret?**, a suspense filled novel about a sassy newswoman who finds herself threatened when she tries to uncover the reasons behind an anchorman's death.

Mary Jane Clark is also a member of FRAXA's Board of Directors and mother of 10-year-old David, who has fragile X. One of the key characters in Mary Jane's novel is a young man who holds the key to the mystery — and has fragile X syndrome. Mary Jane has found a new, creative way to raise awareness of fragile X, and we hope that many, many people will read her book. Mary Jane is currently hard at work on her second novel.

Why Should You Donate Stock to FRAXA Now?

by Michael Tranfaglia MD, Treasurer and Medical Director

By now, you've probably seen lots of ads requesting donations in the form of stocks. Usually these ads mention numerous tax advantages to donating stocks, but they don't ever say exactly what those benefits are. Well, we'd like to explain this in detail, because this really is an exceptional time, and a unique opportunity to donate to FRAXA while also gaining a big tax deduction for yourself.

Let's use a concrete example: suppose you bought $100 worth of stock in Acme Mfg. Corp. five years ago, and that stock is worth $400 now. You could sell that stock now, to avoid the inevitable market correction; you would have to pay capital gains taxes on the $300 profit, which (depending on your tax bracket and the state you live in) would be about $150, leaving you with $250. Or, you could donate that stock, without ever selling it, to FRAXA; you can then deduct the full value ($400) as a charitable donation. Thus, the government will let you keep an extra $200 or so (once again, depending on your income and where you live) that you otherwise would have paid in taxes.

So, you end up with nearly as much in the end by giving the stock away as you would get by selling it! The secret is that you must not sell the stock yourself. By instead transferring it directly to a charitable organization, you never realize a capital gain, and thus you are not liable for the tax.

This is a wonderfully painless way to contribute to fragile X research, so if you're interested, call us — or have your broker call us — to arrange a transfer.

FRAXA POSTDOCTORAL FELLOWSHIPS REQUEST FOR GRANT APPLICATIONS

Upcoming Deadlines: November 1, 1998 and May 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 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. Please contact FRAXA for information or visit the Web at http://www.fraxa.org/. 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 Announces the Second Annual Benefit Gala

featuring author

Mary Higgins Clark

"The Queen of Suspense"

Monday, April 19th

The Four Seasons Hotel, Washington, DC

with Roger Mudd, Master of Ceremonies

Co-chaired by Diane Rehm, National Public Radio Talk Show Host and Mary Beth Busby, FRAXA Vice President and Parent

Tickets: $350 each; $3500 per table of ten. Sponsor: $5000, Research Benefactor: $10,000

Contact either Mary Beth Busby (202-462-2323) or Katie Clapp (978-462-1866)

BE AN ANGEL!

Those wishing to commit to buying or selling a table will be listed on the invitation as members of the Dinner Committee

FRAXA Research Foundation

Member 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: Cristy Hollin, Mary Beth Busby, Michael Tranfaglia and many others

DESIGN: Mary Lou Supple

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+)

FRAXA Research Foundation

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