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A Fragile X Glossary

autism: a complex developmental disability that typically appears during the first three years of life

FMRP: protein necessary for brain development. Production is affected by fragile X syndrome; appears to be involved in synapse maturation and elimination

fragile X syndrome: the most common inherited form of mental retardation. Effects can vary from subtle developmental delays to major impairments

full mutation [of FXS]: is indicated by 200 or more repeats of the DNA sequence mutation; individuals will experience the impairments and delays associated with the syndrome

genotype: the genetic makeup, as distinguished from the physical appearance, of an organism or a group of organisms

hyperarousal: a tendency to become easily overstimulated and to overreact to changes in environment or routines

hyposensitivity: less than the normal ability to respond to stimuli

Individuals with Disabilities Education Act (IDEA): the law that guarantees all children with disabilities access to a free and appropriate public education, and provides services and resources to infants and toddlers with disabilities and their families

phenotypic expression: the observable physical or biochemical characteristics of an organism, as determined by both genetic makeup and environmental influences. In reference to fragile X, refers to how the disorder appears in people's behavior, development, and physical features

premutation carrier [of FXS]: is indicated by 50–200 repeats of the DNA sequence mutation; individuals can transmit the disorder to their children, but may not be affected themselves

vagal tone: an index of neural control of the heart

Going the Distance with Fragile X

ELEVEN YEARS AGO, FPG Child Development Institute (FPG) launched a longitudinal study of a little known form of mental retardation known as fragile X syndrome (FXS). The Carolina Fragile X Project has since grown into a multidisciplinary team studying diverse aspects of the condition, ranging from early identification to school performance. The team's research has led to wide understanding of what constitutes the condition, how it can be detected, strategies for intervention, and how to help families cope.

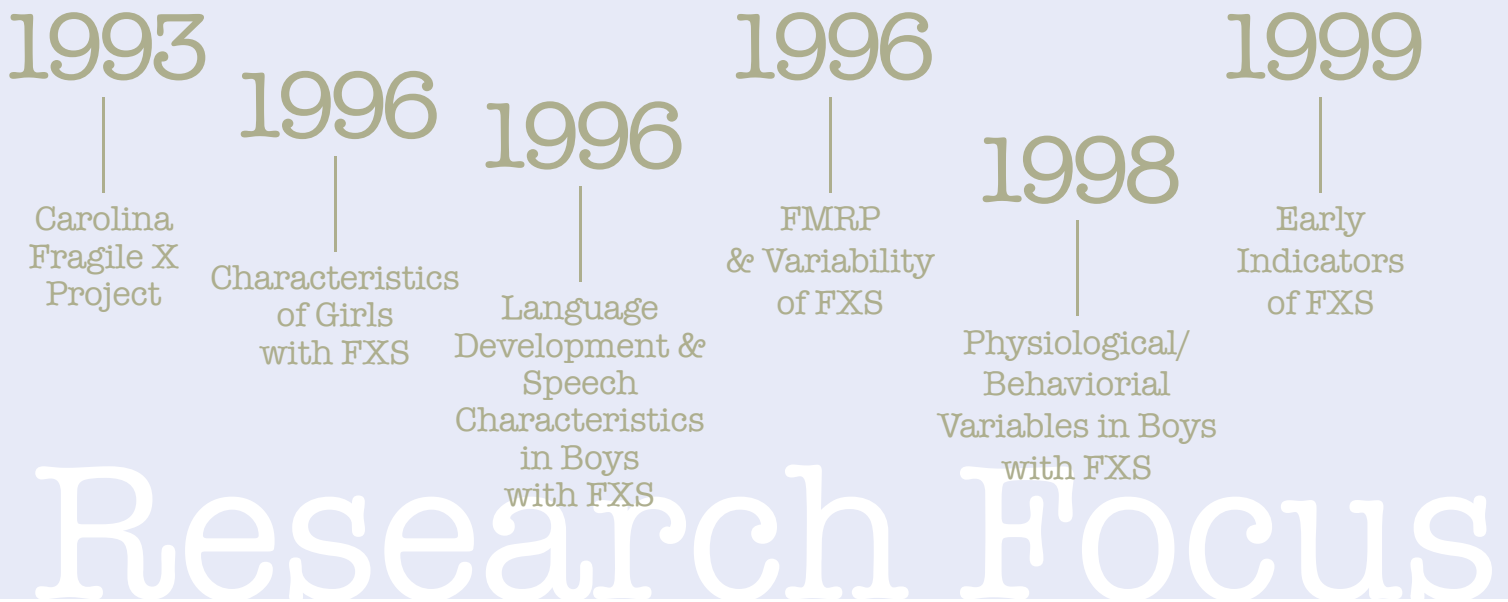
FPG researchers have published thirty-two journal articles and chapters on FXS and many more are in the works. The team is working on seven different grants totaling more than \$2.2 million a year. Next spring, FPG will publish a book on early intervention for young children with FXS. FPG Director Don Bailey has written the definition of fragile X for the online version of the *World Book Encyclopedia*.

"You could say we have put fragile X on the map," Bailey says.

What is fragile X?

Fragile X syndrome is the most common inherited form of mental retardation. First described as Martin-Bell syndrome in 1943, it became known as fragile X syndrome in 1969 when Herbert Lubs discovered an unusual constriction and occasional break at the end of the X chromosome.

In 1991, scientists discovered that FXS results from a mutation known as a trinucleotide repeat expansion, in which a series of three nucleotides (CGG) in the DNA is expanded beyond its normal size. This genetic mutation disrupts



the messages sent to make FMRP, a protein necessary for normal brain development. The normal range of CCG sequences is 5–50 repeats. An individual with 50–200 repeats is a *premutation carrier* of FXS, meaning they can transmit the disorder to their children, but may not be affected themselves. Individuals with 200 or more repeats have the *full mutation* of FXS and will experience the impairments and delays associated with the syndrome.

For individuals with FXS, effects can vary from subtle developmental delays to major impairments. Males with the full mutation are more severely affected than females. Most males will have mild to severe mental retardation with cognitive and communication skills most likely to be affected. They may seem shy, anxious, and inattentive. Hyperarousal, a tendency to become easily overstimulated and to overreact to changes in environment or routines, is a common condition. Males have several distinguishing physical features, including large ears, loose joints and muscles, and an elongated face.

Females generally have milder impairments. About one third will exhibit normal development, another third will exhibit learning disabilities, and about one third will have mental retardation. Females with FXS may also be shy and exhibit social problems.

The early years

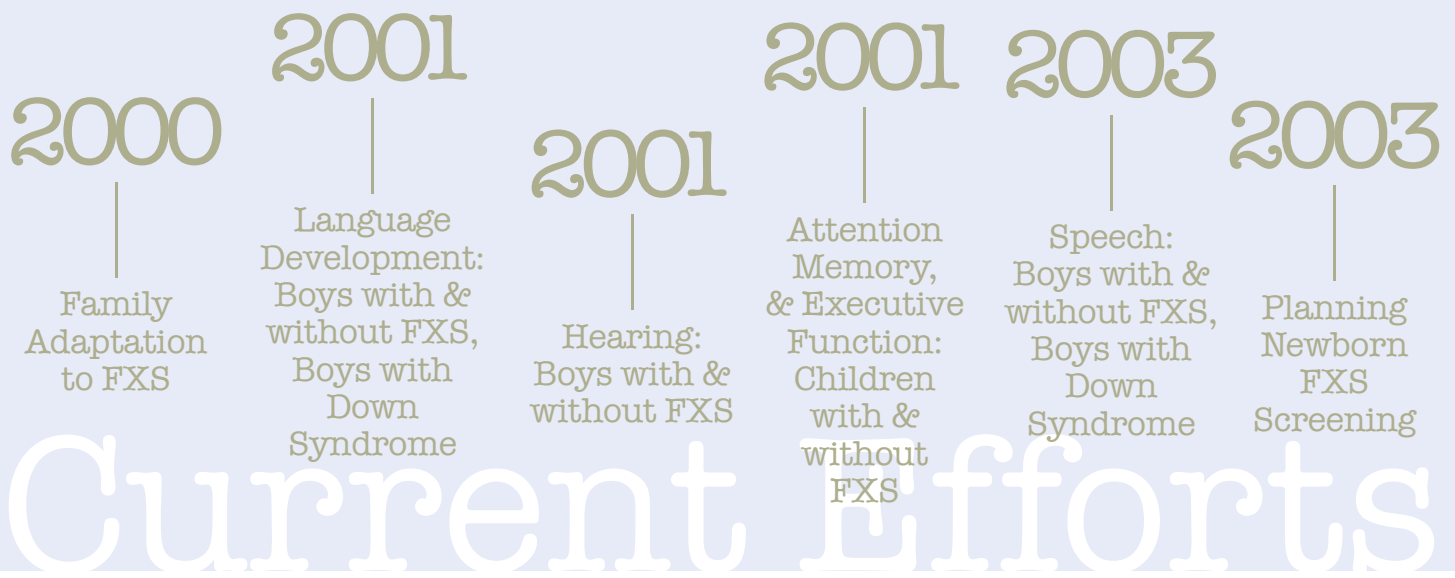
The foundation of the Carolina Fragile X Project began with a series of longitudinal studies following the development of children with FXS beginning in preschool. Initially funded by the Office of Special Education Programs in the US Department of Education, these studies have been headed by Bailey with co-investigator Deborah Hatton. The first

study, begun in 1993, focused on a group of 75 preschool boys. Successive grants in 1995 and 2001 have followed this same group of boys through elementary and middle school. A separate study on young girls was initiated in 1996.

Collectively, those studies have yielded a wealth of information on FXS. They suggest that although parents usually notice problems much earlier, the typical child with FXS is not diagnosed as developmentally delayed until 21 months and not formally diagnosed with FXS until 32 months. They show considerable variability in early development, with some children progressing much faster than others. Boys have been found to have a higher activity level, to be slower to adapt to new situations, to be less persistent and more withdrawn than typical children. Roughly one quarter of boys with FXS are also classified as autistic, and experience more serious delays than children with autism or FXS alone.

Researchers also have collected information about the early intervention or educational services that children with FXS receive, as well as parental perceptions of these services. This work led to a major “synthesis” conference in 2004 where experts discussed the features of an early intervention program most likely to be successful for children with FXS. Researchers are now planning a large study to determine the effectiveness of earlier intervention.

School performance is a crucial part of the longitudinal studies. Analysis of elementary school experiences shows that by second grade, most boys are placed in self-contained classrooms that only serve children with disabilities and that by age 8, many children still experience challenges in performing basic functioning skills. Data on middle school performance are now being collected.



Further refinement and recent studies

Beginning in the mid-90s, FPG researchers began expanding the scope of their research, looking at particular aspects of FXS.

- In a 1996 study funded by the National Institute on Disability and Rehabilitation Research, Joanne Roberts and Penny Mirrett examined the language development and speech characteristics of boys with FXS.
- In another study, Bailey and co-investigators Hatton and Annette Taylor examined the relationship between levels of FMRP, the protein affected by FXS, and the variability in effects of FXS on individuals.
- Bailey and Jane Roberts investigated the relationship between physiological and behavioral variables in boys with FXS.
- In 1998, Jane Roberts received a grant from the FRAXA Foundation to examine classes of medication and their effects on the physiological and behavioral responses of boys with FXS.
- The following year, Bailey, Hatton, Roberts, and Mirrett launched an investigation of the early development of infants, identified the earliest indicators of the syndrome, examined issues related to early screening of infants, and evaluated the usefulness of screening protocols used by pediatricians and other clinicians. This study has led to a planning grant from the NIH to develop a study for newborn screening for FXS.

Since the year 2000, FPG researchers have focused much of their research on children's development and the experience of families of children with FXS.

- Joanne Roberts and co-investigator David Zajac of the School of Dentistry are continuing their research into speech and language with three studies funded by the National Institute of Child Health and Human Development and the March of Dimes. One is studying the language development of three groups of preschool

and early elementary-aged boys—one group with FXS, another with Down syndrome, and one with typical development. The other two projects are examining the hearing, speech, and language development of young boys with FXS compared to young boys without the disorder.

- Bailey and co-investigators Hatton, Stephen Hooper, Peter Ornstein, Jenni Schaaf, and Martie Skinner are midway through a project on Attention, Memory, and Executive Function in FXS. This project seeks to determine how children with FXS attend to important signals in their environment, remember key events and facts, and use this information to make decisions and solve problems.
- Bailey and colleagues were awarded a major center grant from the National Institute for Child Health and Human Development. Entitled Family Adaptation to Fragile X Syndrome, this project seeks to describe and explain the variation in the extent to which parents of children with FXS experience a positive quality of life; construct environments that promote cognitive, language, academic, and adaptive development in their children; and promote social-emotional development and address challenging behaviors in their children with FXS.

“The amazing thing about this research is the many directions it has led us over the years,” says Bailey. “We have learned so much from the children, from families, and from other researchers that has caused us to keep asking new questions and seeking new answers. Our ultimate goal is to do research that helps to shape future policy decisions about early identification and early intervention that provides appropriate support for both children and families.” | [ed](#)

All in the Family



MUCH RESEARCH HAS BEEN CONDUCTED on the underlying biology of fragile X syndrome. Investigators are also well on their way to understanding and describing how FXS affects behavior and development. By comparison, little attention has been paid to the family consequences of fragile X. With the funding of FPG's Fragile X Research Center, that is beginning to change.

The Fragile X Research Center is a joint effort between The University of North Carolina at Chapel Hill and the University of Kansas. Its aim is to understand how families cope with FXS and what might be done to help support families. Eleven investigators from six disciplines—anthropology, developmental psychology, special education, speech and hearing sciences, quantitative psychology, and psychiatry—are collaborating in this effort.

... although a child's learning problems can be hard for families, it is the behavioral problems that are more likely related to serious family stress ...

Why bother to study the family consequences of FXS? "In some respects, the challenges that families of children with FXS face are similar to those of children with other disabilities," says Don Bailey, FPG director and head of the Fragile X Research Center. "But in many ways, the family dimensions of FXS are unique. This is particularly true in the areas of children's learning, their behavior problems, and the inherited aspects of the disease."

Most children with FXS have significant developmental delays that impact school performance and independent functioning. Families must constantly work to organize their home and find specialized services to help their child learn language, cognitive, and academic skills.

Children with FXS may also exhibit a wide range of behavioral and emotional problems, including social anxiety, self-injury, autistic behavior, and other challenging behaviors. Parents must deal with the stress and burden of regulating emotion and problem behavior to help their child adapt to the larger world.

"We've found that although a child's learning problems can be hard for families, it is the behavioral problems that are more likely related to serious family stress," Bailey says. "Families of

children with FXS may not be able to take their child out to a restaurant or the mall without that child acting out in some fashion. That can dramatically alter the family's life."

Bailey says FXS is also unique for families in that it is inherited. Usually parents give birth without realizing they have the gene that carries the disease. Individuals who carry the gene must decide when and how to tell other family members and encourage them to get genetic testing. Women with the gene must consider that they risk having additional children with FXS. Mothers of children with FXS may feel guilty and suffer from depression. Mothers who have the full mutation themselves may face challenges in caring for their children.

The Center is following three broad aims in its research. The first is to describe and explain the extent to which parents of children with FXS experience a positive quality of life, are hopeful for the future, and are protected from adverse mental health outcomes (such as anxiety or depression). The second is to describe and explain the extent to

which parents are able to provide environments that promote their children's cognitive, language, academic, and adaptive development. The third aim is to describe and explain the extent to which parents are able to promote social-emotional development and deal with challenging behaviors.

Center investigators are collaborating on three projects involving a total of one hundred families. Data are being collected using a range of methods, including surveys, semi-structured interviews, ethnographic interviews, and direct observation.

"We aren't just looking at the negative consequences for families," Bailey says. "Many families have rallied together, finding a common purpose in helping their child cope with this disease. In fact, we have met many remarkable families who inspire all of us with the amazing things they have done."

"Ultimately, we are trying to understand why some families do well and others are more challenged," he adds. "Understanding this will help us provide the proper supports to families that need them.

The bottom line is helping them achieve the quality of life for which they hope."

The Fragile X Research Center is funded by the National

Institute of Child Health and Human Development. The Center was awarded \$6 million for a five-year period beginning in July of 2003. |ed|

Acknowledgment: We are grateful to the Hamilton family for sharing photos from their family vacation album for this article.

