



early developments Frank Porter Graham Child Development Institute

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Screening Newborns for Fragile X

KATHY MAY noticed there was a problem with her son, Sam, within weeks of his birth. He was not easy to console and always seemed to keep his hands clasped. At 6 weeks, she tried unsuccessfully to get Sam to look at her when she clapped her hands. At 15 months, Kathy's doctor expressed concern that Sam's language development was behind. She took Sam to an early intervention service provider who, suspecting he was autistic, recommended that he be tested at the local children's hospital. At 20 months, the diagnosis was confirmed—Sam had fragile X syndrome.

Compared to most families of children with FXS, the Mays were fortunate. Sam was diagnosed with FXS earlier than most children. According to a recent FPG study, the average boy with FXS is not diagnosed with FXS until nearly 3 years of age, and many are only identified much later. Had these children been identified earlier, they would have been immediately eligible for early intervention services under the Individuals with Disabilities Education Act.

FPG's study revealed another consequence of the late determination of FXS—more than half of the families surveyed had additional children without knowledge of the reproductive risk. Of the 191 children who were born to these families after the birth of their first child with FXS but before the FXS diagnosis, 109 (57%) also had FXS. Thus, a substantial proportion of the families ended up with two children with the disorder, imposing additional caregiving demands and stress.

“Our study showed that parents perceive the discovery of FXS as a process that takes too long,” says Don Bailey, director of FPG. “One alternative is to establish a program of newborn screening.”

With the discovery that FXS is a genetic disorder and the subsequent development of accurate DNA testing, it is now possible to genetically screen the population for FXS. Possible approaches include screening the following groups: women of childbearing age, pregnant women, newborns, and children at the first sign of developmental delay. FPG researchers have concluded that newborn screening provides distinct advantages over the other options. Whether that policy will become widespread remains to be seen.

In the US, states determine whether to screen newborns for genetic disorders, which disorders to screen for, how to finance screening, and what follow-up mechanisms are in place to provide for treatment and support. Currently, all states mandate screening of newborns for phenylketonuria (PKU) and congenital hypothyroidism, and all states but one screen for galactosemia and sickle cell disease. Beyond that, there is wide variability among the states as to what they screen for.

The question of which disorders to screen for remains the subject of considerable debate among policymakers, medical professionals, and the general public. Currently accepted guidelines rest on three fundamental criteria:

- 1) the disorder must be a significant public health problem that has major consequences for affected individuals,
- 2) an accurate, acceptable, and cost-effective procedure for screening the disorder must be available, and
- 3) a treatment must exist which, if provided early, can significantly alter the course of the disease or disorder.

Bailey contends that FXS clearly meets the first of these criteria and could soon meet the second and third. “A recent review estimates that at least 1 in 4000 males are born with the full-mutation FXS, and 1 in 270 females may be a carrier. FXS exerts a clear and devastating effect on affected individuals, especially males, resulting in moderate to severe mental retardation, high levels of anxiety and arousal, and frequent instances of autism and self-injurious behavior. On that basis, I would contend that FXS presents a significant public health problem.”

With respect to the second criterion, Bailey finds that while DNA testing for FXS is virtually 100% accurate, it is expensive, averaging between \$200–\$300 per test. However, new technologies may soon lower costs considerably. “It is quite likely that the cost of screening could be reduced to \$10–\$20 per child in the next 2–3 years, and other methods could be even cheaper,” he says.

Currently, there are no medical treatments available for FXS, thus, this disorder does not appear to meet the third criterion (a treatment is available) using traditional standards. However, nonmedical treatment by early intervention programs may improve development among individuals with FXS and thus could be considered to alter the course of the disorder. “Recent research suggests that

FMRP, the protein disrupted by FXS, appears to be involved in synapse maturation and elimination,” Bailey says. “If so, the most powerful interventions may be those that could be provided early in life during the period of rapid proliferation and pruning of neural connections.

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“These facts and hypotheses, coupled with the existence of a nationwide system of services readily available for infants with disabilities, provide a strong logical basis in support of early intervention for children with FXS,” Bailey says.

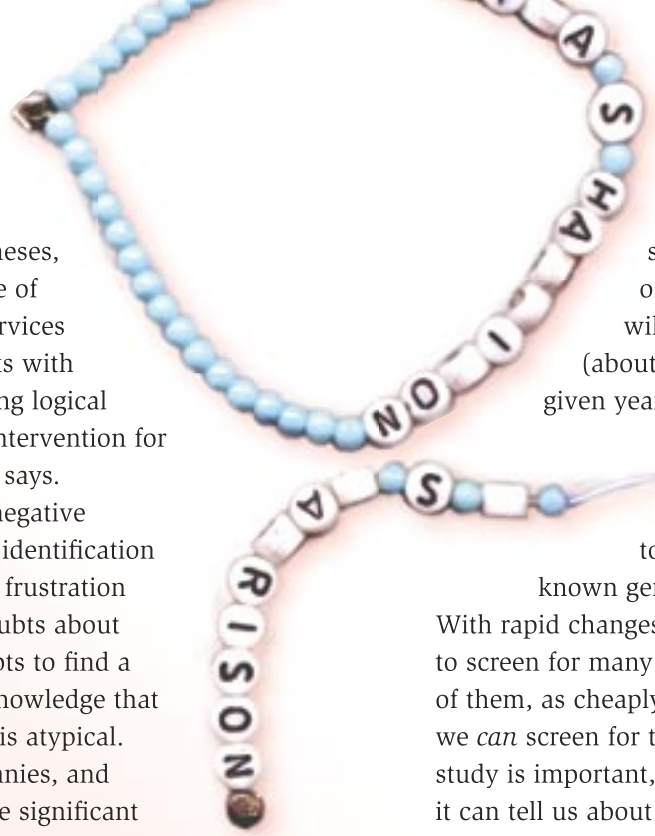
There are a number of negative consequences for delayed identification of FXS. Parents experience frustration with professionals and doubts about themselves in their attempts to find a professional who will acknowledge that their child’s development is atypical. Families, insurance companies, and the health care system face significant financial costs for the repeated visits that often happen before a diagnosis is made. Children and families miss out on the access to early intervention services provided by the Individuals with Disabilities Education Act (IDEA). Finally, families do not have access to information about carrier status of parents and thus may make future reproductive decisions without knowledge of the risk that a child will have FXS.

Nonetheless, routine screening for FXS will not likely happen in the next 3–5 years since it does not fully meet the existing criteria for newborn screening, and also due to concerns about negative consequences for children (e.g., stigmatization), and controversies over issues related to reproductive decision-making and screening for carrier status.

To help make decisions about the desirability of newborn screening, Bailey has embarked on an ambitious project. With planning grants from the National Institute of Health, the Maternal and Child Health Bureau, the Centers for Disease Control and Prevention, and the National Fragile X Foundation, he and his colleagues are developing plans for a massive research project. The goal is to conduct a

study to determine the costs and benefits of newborn screening for FXS. To do so will require screening 1,000,000 newborns (about $\frac{1}{4}$ of all children born in the US in a given year) and conducting follow-up monitoring and intervention studies with those who have FXS.

The Human Genome Project has led to a dramatic increase in the number of known genetic causes of developmental disability. With rapid changes in technology, soon it will be possible to screen for many of these conditions, perhaps hundreds of them, as cheaply and easily as one. But just because we *can* screen for them, does that mean we *should*? “This study is important,” says Bailey, “not only because of what it can tell us about FXS, but also about newborn screening for other disorders. We’re about to enter a new era of genetic information, and research is desperately needed so that when policy decisions are made, they can be informed by solid research.” **ed**



The Behavioral Challenge

WHEN 3-YEAR-OLD JASON WAS PRESENTED WITH A NEW CHILD CARE PROVIDER, he began to bite the back of his own hand. He would not look at the woman, despite his mother's attempts to introduce them. At one point, Jason swung at his mother, hitting her on the leg with his tiny fist.

"I don't know what to do with him when he gets like this," Jason's mother said. "It's making my life really difficult."

According to FPG research, behavior, rather than cognitive delays, may be the greatest concern of parents and teachers of children with fragile X syndrome. Not every child with FXS exhibits serious problems, but many do, and that has prompted the research community to examine how a child's genetics, brain, behavior, and environment act as a result of this single gene disorder.

Deborah Hatton, co-principal investigator of the Carolina Fragile X Project, has been conducting longitudinal studies of temperament and behavior of children with FXS since 1994. Temperament reflects biologically-based individual differences, while behavior reflects how a child acts out his or her feelings. "Temperament and behavior challenges of children with FXS range from shyness to aggression toward others or self, and are more common among boys with the condition than among girls," Hatton says.

Hatton's early studies, based on parent questionnaires completed annually over a 5-year time period, revealed that 3- to 8-year-old boys with FXS are significantly more active and less adaptable, approachable, persistent and intense than typically developing boys of the same age.

"Parents noticed the same behaviors in their boys that we observed during our study: high activity, attention problems, and withdrawing behaviors," Hatton says. "We also found considerable variability in the behavior of boys in the study."

More recently, Hatton's research on boys between the ages of 4 and 12 showed that nearly half (49%) scored within the borderline or clinically significant range on total behavior problems, while more than half (57%) scored in that range on the attention and thought problems. Boys with autistic behavior were more likely to have high scores on thought problems and social problems. Studies show that 25-47% of boys with FXS display autistic behavior.

In her research, Hatton looked for a correlation between maternal education and reported problem behavior. Interestingly, mothers with higher education reported more problem behavior, and thought and attention problems, than did their less educated peers. Boys who were taking medication had more total problem behavior, more internalizing problems, and more social problems. Attention seemed to be an area of particular concern.

Other research found that 73% of boys with FXS met diagnosed criteria for attention deficit hyperactivity disorder (ADHD) compared to 33% of their age and IQ matched peers. Boys with FXS are also likely to engage in self-injurious behavior at some point in their lives. Hatton's colleague Frank Symons found that hand biting is a common form of self-injury in children with FXS, and most likely to be evidenced when the child's preferred routines were disrupted, when requests were made of the child, or when the child was faced with a difficult task.

FPG's research suggests there is an underlying physiological basis for the emotional and self-regulation problems of children with FXS. FPG investigator Jane Roberts has examined the relationships between physiological arousal, as indexed by heart rate variability, and vagal tone (an index of neural control of the heart) in boys with FXS compared to a control group of typically developing boys. Results suggest that boys with FXS have higher heart rates, even when resting. Furthermore, they did not display expected patterns of heart activity in response to phases of increasing challenge. Other researchers have reported that children with FXS displayed elevated levels of electrodermal activity (perspiration measured on finger tips) during a variety of sensory tasks and that they may have higher levels of the stress hormone cortisol. All of this evidence suggests that there may be an underlying physiological basis for the behaviors observed in children with FXS.

FPG's recent work indicates that the temperament and behavior of children with FXS may change radically between infancy and 12 years of age. According to Hatton, infants appear to be *under-responsive* to sensory stimuli, while preschool aged children are *overly responsive*. "In our studies of preschool children, we were struck by their high activity, low attention and adaptability, impulsivity, hypersensitivity to sensory stimuli, and reluctance to approach new people or situations," she says. "In contrast, our clinical impressions of infants with FXS at 9, 12, and 18 months suggests a general hyposensitivity (lack of response) in longitudinal observational protocols of temperament, development, and sensory function."

Families face particular parenting challenges in dealing with children with FXS. Research suggests that parental characteristics and child temperament interact to influence family adaptation and child outcome over time. Positive outcomes occur when families adapt levels of environmental demand to meet the temperamental characteristics of the child, a concept known as "goodness-of-fit." Unresponsive or poor parenting can exacerbate challenging behaviors and the temperamental characteristics of irritability, distress, and negativity.

"A parent who is laid back and calm and who has little structure to daily routines may be well suited to a fussy and highly sensitive infant," Hatton explains. "A parent who is rigid, highly structured, and anxious may find such an infant more challenging."

Recently, FPG has been awarded a grant to study Family Adaptation to Temperament and Challenging Behavior in FXS. Hatton is principal investigator of this project and Steve Reznick is co-principal investigator. Jane Roberts is examining physiology in the children in the study to see how it relates to temperament and behavior.

"The behavior of children with fragile X syndrome is intriguing—particularly the changes that we have observed clinically over time," Hatton says. "The possibility of linking behavior to physiological characteristics, such as heart rate, and to genetic variables, is exciting. While learning more about the behavior of children with FXS, we will

also be searching for strategies that families and teachers can use to promote positive behavior in these children. If behavioral problems are controlled, children will be more likely to experience success developmentally and academically, and parents and teachers will experience less stress. This research has the potential to improve the lives of children and families and the professionals who work with them." |ed|

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