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DARK ENERGY, NEUTRINOS,

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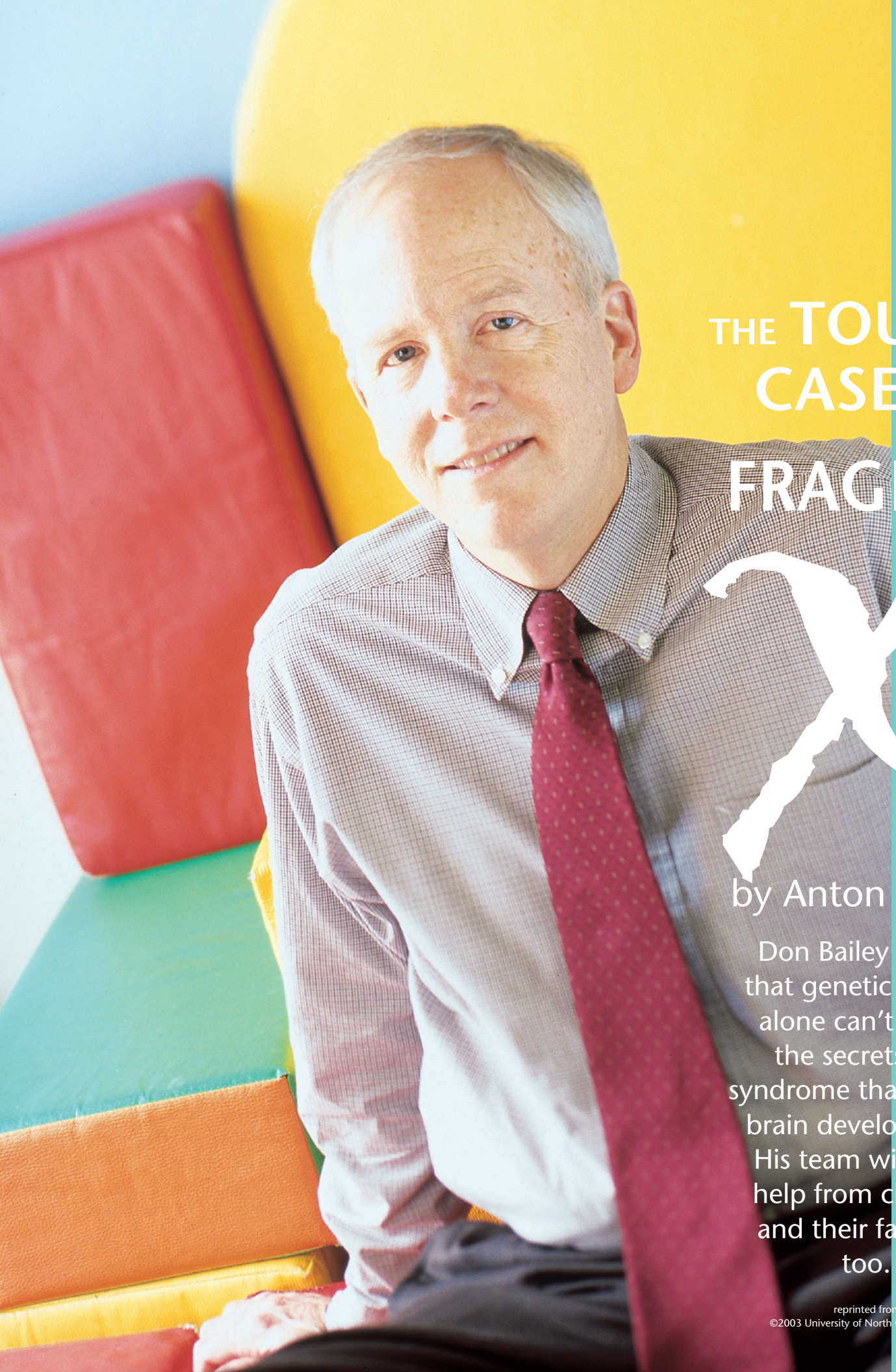

photo by Steve Exum

THE TOUGH CASE OF FRAGILE X

by Anton Zuiker

Don Bailey knows that genetic science alone can't reveal the secrets of a syndrome that impairs brain development. His team will need help from children and their families, too.

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When twelve-year-old Sam May visits Chapel Hill each year, he becomes the center of a genetics dream team. Deep inside each of his X chromosomes is a mutation—a mutation responsible for the delay in Sam's cognitive growth. But Sam clearly understands that the Carolina researchers awaiting his visits are learning valuable lessons from him.

"He loves going there," says his mother, Kathy May. "And when he's done, he asks, 'Has the research helped?'"

Sam has grown up with the researchers at the Frank Porter Graham Child Development Institute (FPG). For ten years he's participated in their studies of fragile X syndrome (FXS), the most common inherited cause of mental retardation. These studies have distinguished the institute, where scientists, physicians, and educators study young children and their families, researching factors that put children at risk for developmental problems.

While other university research centers investigate the basic genetics underlying fragile X, the FPG's Carolina Fragile X Project focuses on child development and how families learn to cope with FXS.

"They're very family-focused," says May, cofounder of the FRAXA Research Foundation, a national advocacy group. Her family's work with FPG has been a positive experience, she says. "I think that they learn a lot from us and from Sam's teachers, and they bring that back into the project."

The institute's researchers are busier than ever, and they are about to embark on a series of new studies that may have implications for other genetic disorders. In a special competition of FXS research centers held by the National Institutes of Health, FPG earned the highest score and a grant for more than $5 million over five years to study parental adaptation to FXS.

"This takes our focus away from the kids alone and looks at the challenges that families face," says Don Bailey, senior scientist and director of FPG. The new grant funds three studies: on how families adapt to the learning needs of their children, to the challenging behaviors of their children, and to the knowledge of their genetic status.

A single gene

In the 1940s, English researcher Julia Bell and Irishman James Purdon Martin noticed that mental retardation can run in families. One condition they identified became known as Martin-Bell syndrome.

Eventually, scientists came to understand that this syndrome had a genetic base. Under a microscope, they noticed that the X chromosomes of Martin-Bell kids looked as if their ends were pinched—some genetic mutation was causing this "fragile" X. This became the new name of the syndrome.

When Bailey first learned about fragile X in the 1980s, the single genetic mutation that causes FXS had yet to be discovered. That came in the early 1990s with the mapping of the human genome and the identification of FMR-1. This gene, on the X chromosome, tells cells to produce a protein that scientists believe is essential for normal brain functioning. One in every 4,000 newborns inherits a mutation in this gene.

Normal FMR-1 genes include a sequence of DNA code, CGG (cytosine-guanine-guanine), repeated 5 to 50 times. This sequence gives instructions to produce the FMRP protein, which helps the brain to develop and function. If that code is repeated 50 to 200 times, the individual is a "premutation carrier" of fragile X syndrome. These individuals are not usually affected, but their children can inherit the full mutation, with more than 200 code repeats. The full mutation inhibits production of the FMRP and leads to mental retardation, behavioral abnormalities, and some physical characteristics such as large ears and a prominent forehead.

While the cause of fragile X is clear, the ways it is expressed in children range considerably. Some children show subtle developmental delays while others have major impairments. Boys with fragile X tend to be more affected than girls.

Bailey says his introduction to the syndrome dovetailed nicely with his earlier work with families, and he's built on that. Since 1992, he's nurtured a multidisciplinary team of researchers, each scientist approaching FXS from a different perspective. "We've got anthropology, speech and language pathology, audiology, neuropsychology, developmental psychology, occupational therapy, and special education," Bailey says. The team is currently working on seven different grants totaling more than $2.2 million per year.

The children

"Our primary focus in the last ten years," Bailey says, "has been on accounting for the variability within fragile X. Why are some kids severely delayed and some are not?"

In 1992, Bailey received his first grant, from the U.S. Department of Education, to study the early development of boys with fragile X. Very little about early development had been described, and children were routinely diagnosed late—after age three—or not at all.

"We also wanted to learn about how families found out about fragile X syndrome, what experiences they had, what signs they had observed," Bailey says. "We wanted to track the kids longitudinally to see what kind of services they were getting and what schools they were placed in." The team started with a group of seventy-five boys in North Carolina, South Carolina, and Virginia and have followed them ever since; these boys are now in late elementary or middle school.

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Courtesy Kathleen May

Sam May, who has fragile X syndrome, in science class with teacher Cathy Thornton.

Bailey's team has accounted for some of the variability in children's development through the study of the protein FMRP. They found that the amount of that protein in the blood does correlate to the level of cognitive development. But this accounts for only part of the severity, so something else must be at work.

Part of the answer may lie in understanding the association between fragile X and a range of other conditions such as anxiety, attention deficits, hyperactivity, and autism. Bailey's team has shown that at least 25 percent of children with FXS also have autism, and that those with autism are much more severely delayed.

Numerous other researchers are striving to find the genetic cause or causes of autism, which is diagnosed through a variety of behaviors. Deborah Hatton was a doctoral student when Bailey received his first grant. She's been deeply involved with the project ever since as a principal investigator and will lead a new study of how families adapt to the temperaments of FXS children.

"Most families and teachers in our sample seem more concerned with behavior problems than with cognitive deficits," she says. "Although we are researchers, we have an obligation to study issues that can improve the quality of life for these children and their families, their teachers, and their therapists."

Kathy May appreciates those efforts. "It's interesting to learn what they see happening to Sam in his life. I get positive feedback that I am doing an okay job with this kid."

Early signs, late detection

The May family, from Fairfax, Virginia, was the first to sign up with Bailey's original study in 1991. Now they're helping him to create an online FXS resource guide, available through the FPG web site and supported by a grant from the Ronald McDonald House Charities.

This web guide will include the developmental and behavioral signs that parents can watch for in their children. These include avoidance of eye contact, nervousness, a long or wide forehead, protruding ears, and limited motor imitation—such as clapping, waving and banging *(see Some signs of fragile X, below, for a longer list)*. A family history of mental retardation, autism, or learning problems is an important warning. And yet, many of these signals can't always be differentiated from other developmental disorders. This lack of clear symptoms makes it difficult to diagnose fragile X accurately.

That's why Bailey recruited occupational therapist Grace Baranek, associate professor of allied health sciences, to the FXS team. Baranek is an expert in detecting early signs of autism through observation of home videos, and Bailey suggested that she apply those skills to the study of FXS.

"We're looking for some early symptoms or behaviors that might be able to help us identify children with fragile X earlier than they're being identified by their pediatricians or other health care providers," Baranek says.

She uses a technique called retrospective video analysis. The families of eleven children previously diagnosed with FXS lent hundreds of hours of their home videos, showing the children during the ages nine

Some signs of fragile X

- A family history of autism, mental retardation, or learning problems

Behavioral problems

- Stiffening of limbs when anxious or excited
- Avoidance of eye contact with parent
- Hand flapping
- Defensive to touch

Social problems

- Limited ability to mimic movements such as clapping, waving, and banging
- Lack of pointing
- Lack of social play

Physical signs

- Long or protruding ears
- Long or wide forehead
- High, arched palate

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to twelve months. Baranek meticulously viewed this footage, looking for autistic behaviors and other developmental delays such as repetitive movements or an unusual posture. "A lot of fragile X children tend to have lower muscle tone," she says.

Baranek's preliminary findings suggest that there are some fragile X symptoms that do show up early, and with these in mind, she's been able to correctly classify 73 percent of the children in the videos. "However, it's always easier to find things in retrospect," she says. Still, she hopes that her work with autism and FXS can identify behaviors that can be translated into a parental questionnaire or an observational form that a pediatrician could use in screening children around age one.

Don Bailey, Jane Roberts, and Deborah Hatton have already proposed one comprehensive checklist that could be useful in detecting FXS in infants and toddlers. But a checklist might not be enough, they suggest.

Newborn screening

Now Bailey and his colleagues are preparing to focus on yet another area, one that will put Carolina prominently at the intersection of genetic research and social policy. The National Institutes of Health awarded a grant to FPG to plan a study involving newborn screening of one million babies for FXS.

While there are hundreds of disorders that can be genetically tested, most states only screen babies for a handful. That's because the traditional criterion for deciding which disorders to screen for has been the availability of a treatment. For example, all states screen for phenylketonuria, a genetic metabolism disorder that leads to mental retardation. A simple dietary change, however, can prevent that, and so the cost of screening is well worth it.

But the Human Genome Project is enabling scientists to screen for hundreds or even thousands of disorders and susceptibilities to diseases. As testing becomes cheaper and consumer demand grows, screening may increasingly tell people about genetic characteristics for which there are no cures.

There is no cure for fragile X syndrome. But newborn screening, says Bailey, could help provide access to early intervention programs. Moreover, it could provide families with important information about their own reproductive risk. In past studies, Bailey learned that more than half of parents have additional children before fully understanding that the first child has the syndrome. Because of this, many families have two children with the full FXS mutation. Parents in the FPG cohort have told Bailey that they wish they had known their own FXS carrier status earlier. "Parents say that the best time to offer genetic screening is preconception," he says.

Steve Exum

Some of the researchers working on fragile X projects at FPG: Front row, from left: Morgan Heath, Anne Wheeler, Jennifer Schaaf, Deborah Hatton, Grace Baranek, Kelly Sullivan, Kathleen Anderson, Joanne Roberts. Back row, from left: Jane Roberts, Peter Ornstein, Caroline Edwards, Anna Williams, Meghan Shanahan, Don Bailey, Penny Mirrett, Steve Reznick, Evie Boswell-Vilt, Lauren Miller, Debra Skinner.

Learning from families

Debra Skinner, a cultural anthropologist, studies how parents make meaning of this genetic disorder and how the knowledge of the disorder affects family relationships. She's especially eager to study the concept of genetic identity—as we increasingly learn to think of ourselves in terms of our genetic instructions, she asks, what can fragile X families teach us?

Bailey says, "We all have multiple identities, but most of us think of genetics as being part of who we are right now. In the next decade, people with a genetic disorder may have that as their defining identity, and that identity will permeate their self-conception."

FXS, with its clear single-gene cause, is a good prototype for other genetic screening, Bailey says. "This puts us in the forefront of many policy issues. Fragile X screening is a model of what's to come."

Meanwhile, other research at Carolina focuses on the biology of FXS. Joe Piven, of the Neurodevelopmental Disorders Research Center and the Department of Psychiatry, in conjunction with researchers at Duke and Stanford universities, received a $3.5 million grant earlier this year to study the brain development of young boys with FXS. The study will use MRI (magnetic resonance imaging) scans at ages two and four to compare fragile X brains with typically developing brains.

Such answers aren't yet available, so Kathy May is making do with her powers of creativity. She's seen that early intervention and developmental therapies—such as special education and home environment training—can be effective. But she and her husband, John, found something easier. Something for their home. Something fun for Sam as well as Mom and Dad.

They bought a trampoline.

"It attracted the neighborhood kids to the back yard," Kathy says. It helped Sam with his balance, and it helped him with his social life. "It was just much more useful than sitting in a therapist's office."

Genetic science uncovered the tiny reasons fragile X syndrome appears in families. But it's the Carolina Fragile X Project that is discovering just how those families live with it, how they bounce back from the shock of learning about the disorder.

"Yes, there have been some extremely difficult times," May says. But when she hears Sam laughing in the back yard, her son doesn't seem disadvantaged at all. e

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