Thanks to dramatic advances in genetics and DNA sequencing technologies, today’s clinicians have increased capabilities to more accurately diagnose inherited diseases. They also now know that disease-causing gene changes, or mutations, often are more common than previously thought.

A team of researchers at the University of California, Davis (UC Davis) studying the rare disease Fragile X syndrome (FXS) found that, indeed, more people have gene changes linked to this disease than anticipated. FXS is an inherited condition caused by changes in a gene on the X chromosome that lead to intellectual disability, behavioral and learning challenges, and various physical characteristics. Previous estimates suggested that FXS affects one in every 2,500 to 8,000 individuals, but it is not known how many people in the general population have the associated genetic changes.

The UC Davis team set out to find a way to determine the prevalence of FXS mutations in the general population before symptoms appear by aiming to show that large-scale newborn screening for FXS mutations was technically and logistically possible and could fill in crucial knowledge gaps. After five years of intensive work and with support from the university’s Clinical and Translational Science Center (CTSI), these researchers made their goal a reality and published findings in the Dec. 21, 2012, issue of Genome Medicine. The National Institutes of Health (NIH) provides funding to the UC Davis CTSI through its Clinical and Translational Science Awards (CTSA) program, which is administered by the National Center for Advancing Translational Sciences (NCATS). NIH’s Eunice Kennedy Shriver National Institute of Child Health and Human Development funded the project with additional support from the Centers for Disease Control and Prevention and the Association for Prevention Teaching and Research.

Using newborn screening to diagnose FXS might enable children with the condition to start treatments earlier, which can improve their quality of life as they get older. Newborn screening is an unbiased way to assess general prevalence of mutations that cause FXS and many other inherited diseases. Identifying mutations at birth can prompt earlier diagnosis and treatment, enable testing for family members who might be affected, and provide those who have mutations but no symptoms with genetic counseling about the risk of passing on the mutation to their children. Having a more accurate prevalence estimate also would help public health officials set aside adequate resources for treatment, patient education and genetic counseling. “This was the very first study in the United States looking at FXS in the general population of newborns,” said Flora Tassone, Ph.D., a professor at the UC Davis Medical Investigation of Neurodevelopmental Disorders (MIND) Institute and lead researcher on the FXS study. “We needed expertise for designing the study and for collecting and analyzing the data on the overall prevalence of FXS mutations.”

To meet that need, Tassone’s team turned to Danh Nguyen, Ph.D., who was then the associate director of the Biostatistics, Epidemiology and Research Design (BERD) unit at UC Davis’ CTSI and current director of the BERD unit at UC Irvine. Among many critical resources, CTSA institutions offer expertise in study design and data collection and analysis that can help speed research progress. “Nguyen and the CTSA-supported BERD unit were key players in designing the study,” Tassone said. “Without them, I don’t think we could have done this research.”

UNDERSTANDING A RARE DISEASE
CTSA Resources Support Largest U.S. Newborn Screening Study for Fragile X Mutations

NCATS supports research aimed at improving knowledge of and finding treatments for rare diseases, including FXS. In most FXS patients, a specific DNA segment is expanded within the Fragile X Mental Retardation 1 (FMR1) gene on the X chromosome. Normally, this DNA segment repeats from five to about 44 times. In people with FXS, however, the segment repeats more than 200 times and is called a full FMR1 mutation. The abnormal segment turns off the FMR1 gene, and as a result, cells do not produce enough of a protein necessary for proper nervous system function, leading to FXS symptoms.

Some people who do not have the full mutation can still have an abnormal number of repeats, which can produce a variety of symptoms. People with 55 to 200 repeats are said to have the FMR1 gene premutation, and people with 45 to 54 repeats have gray zone, or intermediate, expansions. Individuals with a premutation have normal functioning, but sometimes they have autism spectrum disorders, attention deficit-hyperactivity disorder, depression, anxiety, a form of premature menopause and a neurological condition resembling Parkinson’s disease. People who fall within any of these categories — full mutation, premutation or gray zone expansion — can pass on these genetic changes to their children.

A TEAM-BASED APPROACH TO THE PROBLEM OF PREVALENCE

Team-based models like the one at the UC Davis CTSC ensure research projects benefit from knowledge and expertise not otherwise available to a single researcher. For this study, the researchers wanted to carry out a large-scale newborn screening pilot study, but they were unsure of how to design the study and analyze the data. Biostatisticians in the CTSC’s BERD unit provided the statistical expertise necessary for planning and analyzing data from population studies of this size and scope.

An NICHD grant enabled the researchers to establish screening sites in three locations: University of North Carolina Hospital in Chapel Hill, led by Don Bailey, Ph.D., of RTI International; Rush University Medical Center in Chicago, led by Elizabeth Berry-Kravis, M.D., Ph.D.; and UC Davis Medical Center. For each newborn in the study, the team collected a few drops of blood, which were stored on filter paper. Across the three sites, Tassone and her team ultimately collected 14,207 male and female newborn blood spot samples.

Coordinating study personnel and data collection across three sites in opposite corners of the country required superb attention to detail. With their epidemiologic and biostatistical expertise, staff from the BERD unit provided much-needed support to the clinical team for “monitoring data collection and making sure that the data were of the quality needed for the analysis,” Nguyen explained.

With the data collection and blood analysis complete, Nguyen set about analyzing the data. The results revealed that one in 66 females and one in 112 males carried the gray zone expansion. The premutation occurred in one in 209 females and one in 430 males. The data set was too small to detect the prevalence of the full mutation in the general population, but the study’s findings on the premutation and gray zone carriers add important new information to the FXS knowledge base.

“BERD’s role in this study was integral to this research project,” said Tiina Urv Ph.D., health scientist administrator at NICHD. “The newborn screening pilot program was a great example of research collaboration. Every person on the research team focused on what they did best. By doing this and by using multiple available resources the scientific process was able to move forward efficiently and effectively.”

IMPLICATIONS FOR FAMILY AND PUBLIC HEALTH

Identifying FXS premutation carriers has implications beyond just their own clinical futures. “When you identify a baby with the premutation, you identify a whole family that may have a different kind of involvement,” said Randi Hagerman, M.D., UC Davis’ MIND Institute Director and last author on the study.

For this reason, MIND Institute researchers have begun recruiting affected family members of screened newborns to participate in ongoing clinical trials. The clinical resource component of the UC Davis CTSC has a hand in this stage of the effort as well. “The CTSC is critically important for the follow-up work we do with the family members, helping us with all of our treatment trials,” Hagerman said. “This work is opening up whole new areas of clinical involvement and allowing us to evaluate premutation carriers in much greater detail.”

In addition to the family member follow-up, the multidisciplinary collaborations that enabled the screening study have led to other ongoing research. One such effort, which involves Tassone and other screening study authors, involves checking up on the screened infants when they are 18-24 months old. “In light of this pilot study, it is important to confirm and demonstrate that we see symptoms early in life in the premutation carriers,” Tassone
said. "We are seeing different developmental characteristics between carriers and non-carriers."

This pilot study, which began by collecting prevalence data, now has set the stage for a more comprehensive examination of the clinical consequences of FXS-related gene changes. Tassone and Hagerman hope to conduct a larger screening study soon that will confirm the findings of the initial study, follow the identified premutation carriers over a longer period of time and determine the prevalence of the full mutation in the general population.