the Fragile X Research & Treatment Center

WHAT IS FRAGILE X?

It is estimated that 1 in 129 females in the general population carry the fragile X premutation and that one in 3,600 individuals have the full mutation resulting in fragile X syndrome.

Fragile X syndrome is the most common cause of inherited mental impairment, which can range from learning disabilities to severe cognitive or intellectual disabilities. Fragile X syndrome is also the most common single-gene cause of autism.

Fragile X associated tremor-ataxia syndrome (FXTAS) is a condition that causes balance, tremor and memory problems in some older male carriers of the fragile X premutation. The fragile X research team at the M.I.N.D. Institute discovered FXTAS in 2001.

Fragile X-related premature ovarian failure (POF) is a problem with ovarian function that can lead to infertility and early menopause prior to age 40 in some female premutation carriers.

The M.I.N.D. Institute established the Fragile X Research and Treatment Center in 2001. The center unites research studies with clinical evaluations to achieve two important goals:

- Support important advances in our understanding of fragile X
- Develop interventions that improve the quality of life for people with fragile X syndrome and related conditions, including fragile X-associated tremor ataxia syndrome (FXTAS) and premature ovarian failure (POF).

Led by experts in clinical medicine and molecular biology

Randi Hagerman, medical director of the M.I.N.D. Institute and director of the Fragile X Research and Treatment Center, is a physician with more than 25 years of experience in the field of neurodevelopmental disorders and fragile X syndrome. She occupies the Endowed Chair in Fragile X. Her research focuses on the treatment of conditions related to the fragile X gene mutation and understanding how the molecular changes lead to clinical involvement. She also has a strong clinical and research interest in autism and has conducted research examining the association between autism and fragile X syndrome.

Paul Hagerman, a physician and molecular bioscientist, heads the molecular laboratory of the center and carriers out cutting-edge research in fragile X syndrome and FXTAS. His work examines the DNA, RNA and proteins related to these disorders.

A multi-disciplinary approach

The center includes specialists in pediatrics, molecular genetics, psychiatry, psychology, neurology, genetic counseling, speech and language pathology, occupational therapy, neurobiology, pathology, functional magnetic resonance imaging and social work. This team has evaluated children and adults with fragile X syndrome and carriers with the premutation from across the United States and throughout the world.

CURRENT STUDIES

Research in **genotype-phenotype correlations in fragile X families** involves studying associations between molecular variations in the fragile gene and the physical and behavioral and cognitive features of both children and adults affected with fragile X syndrome and in those who carry the premutation form of the gene.

Fragile X-associated tremor/ataxia syndrome research involves evaluation of men who are 40 years of age and older who have the premutation and their brothers who do not have the premutation. Assessments include neuropsychological and neuroimaging studies.

One study considers whether the responsiveness of the amygdala to social stimuli leads to the **anxiety and avoidance** hallmark behaviors of fragile X patients. This research also investigates whether the increased anxiety contributes to autistic behaviors, such as deficits in reciprocal social behavior, in children with the syndrome.

Assistive technology research evaluates the efficacy of specialized software for enhancing written language expression in individuals with fragile X, autism, sex chromosomal abnormalities and other disorders.

RESEARCH RESULTS

Several proteins have been identified that may be related to the onset of fragile X-associated tremor ataxia syndrome (FXTAS). Of these proteins **lamin A/C** will be singled out for further study, given its implications in similar brain disorders, including Charcot–Marie–Tooth disease.

Increased risks for **autism spectrum disorders, attention deficit hyperactivity disorder, social deficits and learning disabilities** have been identified in both children who are carriers of the fragile X premutation and in children with the full fragile X mutation.

FXTAS research has shown that the CGG repeat number correlates with the **degree of neuropathology and the age of onset.**

Physicians now have specific standards to use when deciding whether or not to **screen patients** for fragile X syndrome, FXTAS and POF.

Studies have shown that **ampakines** are not effective in treating fragile X syndrome or autism, but studies using new targeted treatments for fragile X syndrome and FXTAS are being planned.

SUPPORT

The National Institutes of Child Health and Development (NICHD) provides funding for the center in collaboration with the University of Washington in Seattle. Individual research projects are funded by NICHD, the National Institute of Neurological Disorders and Stroke, the Coleman Foundation, National Institutes on Disability and Rehabilitation Research, the Centers for Disease Control and private philanthropy.

About the UC Davis M.I.N.D. Institute

The UC Davis M.I.N.D. (Medical Investigation of Neurodevelopmental Disorders) Institute is a unique, collaborative center bringing together parents, scientists, clinicians and educators for research on autism, fragile X syndrome, learning disabilities and other neurodevelopmental disorders.

For more information about the Fragile X Research & Treatment Center, please contact:

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the Cognitive Analysis & Brain Imaging Laboratory

KEY OUTCOMES TO DATE

- Better understanding of the neural structures and connective patterns that underlie cognitive functions
- State-of-the-art images of differences in brain structure
- Enhanced knowledge of why children with neurodevelopmental disorders tend to have difficulties with numerical and visuospatial thinking
- Evidence of possible common neurocognitive bases for those difficulties in several populations of children with different genetic disorders
- Emerging pictures of the relationship of cognitive impairments to behavioral and psychiatric disorders
- Progress toward the identification of new interventions that reduce or eliminate challenges for children with genetically based disorders

A research lab with a new approach

The Cognitive Analysis and Brain Imaging Laboratory at the UC Davis M.I.N.D. Institute investigates genetically based neurodevelopmental disorders. The lab is distinct in that it adopts a cognitive neuroscience approach to such disorders by combining the analytical methods of cognitive psychology with current brain imaging techniques to arrive at more complete explanations of the cognitive impairments manifested by children with chromosome 22q11.2 deletion syndrome, fragile x syndrome and similar conditions. The lab's goal is to use that explanatory knowledge to design multimodal interventions that reduce, or even eradicate, those impairments.

The assessments

Children who visit the lab for research studies participate in two main types of assessments. One is cognitive analysis, involving computer games that test the functioning of specific brain circuits under different conditions and predict characteristic patterns of performance. (See examples of the analytical tests at **cabil.mindinstitute.org**.)

The other assessment involves safe, radiation-free and state-of-the-art neuroimaging methods—functional magnetic resonance imaging, voxel based morphometrics and diffusion tensor fiber tracking—to characterize changes in the brain's neural structure, connectivity and function. In collaboration with other labs, genetic analyses are also conducted to more fully explain the biological basis of the atypical patterns of brain and cognitive development.

Led by a specialist in cognitive neuroscience

Tony J. Simon is an associate professor of psychiatry and behavioral sciences. His research focuses on the neural basis of cognitive impairments that result in mental retardation, developmental disabilities and psychopathology. Building on his influential theory of the visuospatial foundations of numerical competence, Simon investigates how dysfunction in specific neurocognitive processing systems, such as attention and spatial cognition, can generate a range of cognitive and behavioral impairments.

ABOUT GENETICALLY BASED NEURODEVELOPMENTAL DISORDERS

Research at the Cognitive Analysis and Brain Imaging Laboratory includes children ages 7-to-14 with a genetically based disorder such as:

Chromosome 22q11.2 deletion syndrome, also called velocardiofacial syndrome and DiGeorge syndrome, is caused by the deletion of a small segment of the long arm of chromosome 22 and is linked to over 180 physical, psychological and behavioral anomalies. Children with the syndrome experience some degree of developmental delay and learning difficulties. Most of these children have at least some of the following physical conditions: congenital heart defects, cleft palate, immune deficiencies or problems with calcium regulation. Likewise, most of them are at increased risk for some of the following behavioral and psychological disorders: attention deficit hyperactivity disorder, autism spectrum disorders, oppositional-defiant disorder, obsessive-compulsive disorder and schizophrenia.

Fragile X syndrome is the most common cause of inherited cognitive impairment. Its outcomes range from learning disabilities to more severe cognitive or intellectual disabilities. It is the most common known cause of autism. Symptoms also can include characteristic physical and behavioral features, delays in speech and language development and learning difficulties in numerical and mathematical domains.

Turner syndrome is a chromosomal condition that describes girls and women with common features that are caused by complete or partial absence of the second sex chromosome. The syndrome occurs when one of the two X chromosomes normally found in females is missing or contains certain structural defects. Almost all people with Turner syndrome have short stature and loss of ovarian function, but the severity of these problems varies considerably amongst individuals. Learning difficulties in spatial, numerical and mathematical domains are common.

Williams syndrome is characterized by mild to moderate mental retardation or learning difficulties, a distinctive facial appearance and a unique personality that combines overfriendliness and high levels of empathy with anxiety. The most significant medical problem associated with the syndrome is cardiovascular disease caused by narrowed arteries. By age 30, many individuals with the syndrome have diabetes or pre-diabetes and mild to moderate sensorineural hearing loss. Compared with strengths in verbal expression and auditory memory, individuals with Williams syndrome exhibit considerable weakness with spatial and numerical cognition.

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