
Randi J. Hagerman, M.D.

Hagerman, Randi J., M.D. *Medical Director, WE'Fcxku'M.I.N.D. Institute; Endowed Chair in Ht ci kg'Z'Research; Professor, Department of Pediatrics, School of Medicine*

Biography

Dr. Randi Hagerman is a Developmental and Behavioral Pediatrician and the Medical Director of the M.I.N.D. Institute at UC Davis. She is internationally recognized as both a clinician and researcher in the fragile X field. Dr. Hagerman received her M.D. from Stanford University where she also carried out her Pediatric residency. She completed a Fellowship in Learning and Disabilities and Ambulatory Pediatrics at UC San Diego and, subsequently, spent the next 20 years from 1980 to 2000 at the University of Colorado where she headed Developmental and Behavioral Pediatrics. She co-founded the National Fragile X Foundation in 1984 in Colorado and developed a world-renowned fragile X research and treatment center. In 2000, Professor Hagerman moved to UC Davis to be the Medical Director of the M.I.N.D. Institute. Dr. Hagerman and her team discovered the Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) which is a neurological disorder that affects older male and rare female carriers of fragile X. Dr. Hagerman's research involves genotype-phenotype correlations in fragile X and she carries out this research in collaboration with her husband, Paul Hagerman, M.D., Ph.D. Professor Randi Hagerman has written over 150 peer-reviewed articles and numerous book chapters on neurodevelopmental disorders. She has written several books on fragile X including a 3rd Edition of *Fragile X Syndrome: Diagnosis, Treatment, and Research* which was published in 2002 by Johns Hopkins University Press. Dr. Hagerman has received numerous awards for her research in fragile X syndrome including the Jerrett Cole Award from the National Fragile X Foundation for unselfish dedication to work with fragile X children and adults, the Bonfils-Stanton Foundation Award for Science including Medicine, the IASSID Distinguished Achievement Award for Scientific Literature, the 2005 Distinguished Scholarly Public Service Award from UC Davis, and the 2006 Dean's Award for Outstanding Mentoring at UC Davis. In 2004, to honor both Randi and Paul Hagerman in recognition of their work in FXTAS, the National Fragile X Foundation established the Hagerman Award. This award recognizes research accomplishments in the field of FXTAS and is given at the bi-annual International Conference on Fragile X. Dr. Hagerman has worked internationally to establish fragile X clinical programs and research programs throughout the world.

Publications

Adams JS, Adams PE, Nguyen D, Brunberg JA, Tassone F, Zhang W, Koldewyn K, Rivera SM, Grigsby J, Zhang L, DeCarli C, Hagerman PJ, **Hagerman RJ**. Volumetric brain changes in females with fragile X-associated tremor/ataxia syndrome (FXTAS). *Neurology* 69:851-859, 2007. *This is the first paper to show female abnormalities in FXTAS.*

Brega AG, Goodrich G, Bennett RE, Hessler D, Engle K, Leehey MA, Bounds LS, Paulich MJ, **Hagerman RJ**, Hagerman PJ, Cosgwell JB, Tassone F, Reynolds A, Kooker R, Kenny M, Grigsby J. The primary cognitive deficit among males with fragile X-associated tremor/ataxia syndrome (FXTAS) is a dysexecutive syndrome. *J Clin Exp Neuropsychol* 15:1-17, 2008. *Documentation of primacy of frontal deficits in premutation carriers.*

Amiri K, **Hagerman RJ**, Hagerman PJ. Fragile X-Associated Tremor/Ataxia Syndrome: An Aging Face of the Fragile X Gene. *Arch Neurol* 65(1):19-25, 2008. *Overall review to synthesize recent findings.*

Soontarapornchai K, Maselli R, Fenton-Farrell G, Tassone F, Hagerman PJ, Hessler D, **Hagerman RJ**. Abnormal Nerve Conduction Features in Fragile X Premutation Carriers. *Arch Neurol* 65(4):495-498, 2008. *First to show abnormal nerve conduction in premutation carriers.*

Hagerman RJ, Rivera SM, Hagerman PJ. The Fragile X Family of Disorders: A Model for Autism and Targeted Treatments. *Current Pediatric Reviews* 4:40-52, 2008. *Review of fragile X and autism.*

Coffey S, Cook K, Tartaglia N, Tassone F, Nguyen D, Pan R, Bronsky H, Yuhas J, Borodyanskaya M, Grigsby J, Doerflinger M, Hagerman P, **Hagerman R**. Expanded Clinical Phenotype of Women with the FMR1 Premutation. *Am J Med Genetics Part A* 146A:1009-1016, 2008. *First to document fibromyalgia and hypothyroidism in female carriers.*

Greco CM, Tassone F, Garcia Arocena D, Tartaglia N, Coffey SM, Vartanian TK, Brunberg JA, Hagerman PJ, **Hagerman RJ**. Clinical and neuropathological findings in a woman with the FMR1 premutation and multiple sclerosis. *Arch Neurol* 65(8):1114-6, 2008. *Documentation of FXTAS and MS together opening up a new association.*

Angkustsiri K, Wirojanan J, Deprey LJ, Gane LW, **Hagerman RJ**. Fragile X Syndrome with Anxiety Disorder and Exceptional Verbal Intelligence. *Am J Med Genet Part A*:146A:376-379, 2008. *Case of gifted cognition with emotional problems and learning disabilities which expands the fragile X spectrum of involvement.*

Wirojanan J, Angkustsiri K, Tassone F, Gane LW, **Hagerman RJ**. A girl with fragile X premutation from sperm donation. *Am J Med Genet A* 146(7):888-892, 2008. *Case to promote the need of sperm screening for fragile X.*

Grigsby J, Brega AG, Engle K, Leehey MA, **Hagerman RJ**, Tassone F, Hessler D, Hagerman PJ, Cogswell JB, Bennett RE, Cook K, Hall DA, Bounds LS, Paulich MJ, Reynolds A. Cognitive Profile of Fragile X Premutation Carriers with and without Fragile X-Associated Tremor/Ataxia Syndrome. *Neuropsychology* 22(1):48-60, 2008. *Study documents neuropsychological deficits of premutation carriers with and without FXTAS.*

Leehey MA, Berry-Kravis E, Goetz CG, Zhang L, Hall DA, Li L, Rice CD, Lara R, Cogswell J, Reynolds A, Gane L, Jacquemont S, Tassone F, Grigsby J, **Hagerman RJ**, Hagerman PJ. FMR1 CGG repeat length predicts motor dysfunction in premutation carriers. *Neurology* 70(16 Pt 2):1397-402, 2008. *Documentation of CGG predictor for onset of FXTAS symptoms.*

Wirojanan J, Kraff J, Hawkins DS, Laird C, Gane LW, Angkustsiri K, Tassone F, **Hagerman RJ**. Two Boys with fragile X syndrome and Hepatic Tumors. *J Pediatr Hematol Oncol* 30(3):239-41, 2008. *Documentation of 2 cases with rare hepatic cancer in FXS.*

Aguilar D, Sigford KE, Soontarapornchai K, Nguyen DV, Adams PE, Yuhas JM, Tassone F, Hagerman PJ, **Hagerman RJ**. A quantitative assessment of tremor and ataxia in FMR1 premutation carriers using CATSYS. *Am J Med Genet A* 146(5):629-635, 2008. *Demonstration of motor problems in non FXTAS premutation carriers.*

Jenkins EC, Tassone F, Ye L, Gu H, Xi M, Velinov M, Brown WT, **Hagerman RJ**, Hagerman PJ. (2008) Reduced telomere length in older adult males with premutation alleles of the fragile X mental retardation 1 gene. *Am J Med Genet Part A*. 146A:1543-1546, 2008. *Documentation of short telomeres in premutation carriers and possible molecular mechanisms involved.*

Koldewyn K, Hessel D, Adams J, Tassone F, Hagerman PJ, **Hagerman RJ**, Rivera SM. Reduced Hippocampal Activation During Recall is Associated with Elevated *FMR1* mRNA and Psychiatric Symptoms in Men with the Fragile X Premutation. *Brain Imaging and Behavior* 2:105-116, 2008. *Adults with the premutation have reduced hippocampal activity so CNS abnormality even in young adult pre males.*

Brouwer JR, Severijnen E, de Jong FH, Hessel D, **Hagerman RJ**, Oostra BA, Willemsen R. Altered hypothalamus-pituitary-adrenal gland axis regulation in the expanded CGG-repeat mouse model for fragile X-associated tremor/ataxia syndrome. *Psyneun* 33, 863-873, 2008. *Documentation of elevated cortisol in premutation mice.*

Tartaglia N, Davis S, Hench A, Nimishakavi S, Beauregard R, Reynolds A, Fenton L, Albrecht L, Ross J, Visootsak J, Hansen R, **Hagerman R**. A New Look at XYY Syndrome: Medical and Psychological Features. *Am J Med Genet Part A* 146A:1509-1522, 2008. *The largest study yet of medical and emotional problems in XYY males and guidance about treatment.*

Seritan A, Nguyen D, Farias S, Hinton L, Grigsby J, Bourgeois J, **Hagerman R**. Dementia in Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS): Comparison with Alzheimer's Disease. *Am J Med Genet B Neuropsychiatr Genet*. 2008, Epub ahead of print. *First paper to compare Alzheimer's and FXTAS.*

Kogan CS, Turk J, **Hagerman RJ**, Cornish KM. Impact of the fragile X mental retardation 1 (*FMR1*) gene premutation on neuropsychiatric functioning in adult males without fragile X-associated tremor/ataxia syndrome: A controlled study. *Am J Med Genet B Neuropsychiatr Genet* 2008, Epub ahead of print. *Controlled study of neuropsych deficits in carriers without FXTAS.*

Presentations

New Developments in FXTAS, UCSF Memory and Aging Center and UCSF Autism and Neurodevelopment Center Seminar Series, San Francisco, CA, June 2008.

Fragile X Syndrome, NFXF Missouri Parent Support Group, St. Louis, MO, June 2008.

Advances in FXTAS Research, RNA and Disease: RNA Metabolism and Associated Pathologies Conference, Rome, Italy, June 2008.

Targeted Treatments for Fragile X Syndrome and an Update on Premutation Involvement, Northern California Annual Clinical Genetics Exchange, Kaiser Permanente, Sacramento, CA, May 2008.

Immuno Profile in Fragile X and Autism, 2008 IMFAR (INSAR), London, England, May 2008.

ASD Treatment: Developing Research Priorities for Evidence-based Practices (Panel), Interagency Autism Coordinating Committee, NIEHS, Town Hall, Sacramento, CA, May 2008.

Understanding the Neurobiology of Fragile X Syndrome (Keynote Speaker), Human Development Center (HDC) Institute Conference, Louisiana State University Health Science Center, New Orleans, LA, April 2008.

Psychopharmacologic Treatment of Autism and Fragile X Syndrome, Human Development Center (HDC) Institute Conference, Louisiana State University Health Science Center, New Orleans, LA, April 2008.

Finding a Career in Neurodevelopmental Disorders, Physician Speaker Series, American Medical Student Association at American River College Pre-Med Chapter, Sacramento, CA, April 2008.

Fragile X Syndrome, Fragile X Awareness Day 2008, California State Capitol, South Steps, Sacramento, CA, April 2008.

Fragile X Syndrome and FXTAS, Translational Research Course in Neurodevelopmental Disorders, UC Davis Center for Neuroscience, Sacramento, CA, April 2008.

Fragile X: Expansion of a Genetic Disorder, The Spectrum of Developmental Disabilities XXX: Neurobehavioral Syndromes, Johns Hopkins University, Baltimore, MD, March 2008.

Fragile X: A Family Affair with New Targeted Treatments, Fragile X Syndrome Treatment Update and Practical Interventions, Elwyn Genetics, Elwyn, PA, April 2008.

Fragile X Syndrome & FXTAS: Two Faces of the Fragile X Gene, Psychiatry Grand Rounds, Alta Bates Herrick Hospital, Berkeley, CA, March 2008.

Quantitative Measures of CNS Function in Fragile X Syndrome, FRAXA 2008, Banbury Center, Cold Spring Harbor, NY, March 2008.

Clinical Research with the Consortium, Clinics Consortium Meeting, Atlanta, GA, March 2008.

1st talk) Lessons in Fragile X and Autism; 2nd talk) New Treatments for Autism and Fragile X; 3) Aging and FXTAS, Fourth Congress of Special Education in Guatemala, Central America, Panama and the Caribbean “Opening Doors... Discovering Worlds”, Guatemala City, Guatemala, February 2008.

Translational Research in Fragile X, Translational Research Meeting, Research Seminar Series, M.I.N.D. Institute, Sacramento, CA, February 2008.

Quantitative Measures of CNS Function for Targeted Treatments, Novartis, Geneva, Switzerland, February 2008.

Fragile X: A Family Affair, Minds Behind The M.I.N.D. Lecture Series, M.I.N.D. Institute, Sacramento, CA, January 2008.

Living with Fragile X, Community Lecture, Santa Cruz, CA, January 2008.

How I Involve Others in Clinical Research, Clinical Research Vignette, UC Davis Department of Pediatrics Retreat, Sacramento, CA, January 2008.

Fragile X: A Family Affair and Targeted Treatments, UCLA Grand Round, Los Angeles, CA, January 2008.

Fragile X: A Family Affair including autism, FXTAS, and premature ovarian failure, Kaiser Fontana, Ontario, CA, December 2007.

Fragile X: A Family Affair, National Centre for Biological Sciences, Bangalore, India, December 2007.

New Treatments in Fragile X Syndrome, Chennai Conference, Chennai, India, December 2007.

1st talk) Beyond FXTAS: Treatment implications for carriers; 2nd talk) Lessons in neurobiology, autism and neurodegeneration, II Balear Fragile X Conference, Palma de Mallorca (Islas Baleares), Spain, November 2007.

Fragile X Syndrome and FXTAS, UC Davis Guest Lecture Human Genetics MCB 162, Davis Campus, Davis, CA, November 2007.

Fragile X: A Family Affair, FX Conference, Cincinnati, OH, November 2007.

The continuum of involvement from the premutation to the full mutation, Fragile X-Related Syndromes: From Molecular to Clinical Approach (Conference), Baeza, Spain, October 2007.

Characterization of the Neuropathy in FXTAS, 13th Fragile X and XLMR Workshop, Venezia Lido, Italy, October 2007.

1st talk) Autism: New Advances in the Genetics of Autism and Fragile X; 2nd) Neurodevelopmental Disorders Causing ADHD, 36th Annual Montrose Fall Clinics CME Program, Montrose Memorial Hospital, Montrose, CO, September 2007

Pharmacotherapy in Children with Autism and Fragile X Syndrome, Autism and Fragile X Conference, Yuwaprasart Waithayopatum Child Psychiatric Hospital, Siam City Hotel, Bangkok, Thailand, September 2007.

Treatment of Difficult Cases, National Fragile X Awareness Day Webcast, Denver, CO, July 2007.

Behavioral Genetics, Mountain States Genetics Regional Collaborative Center, Denver, CO, July 2007.

Research Funding

Principal Investigator: Genotype-Phenotype Relationships in Fragile X Families, NICHD, 06/15/98 to 03/31/12, \$391,109 annual direct. *The overall focus of this project is to explore both the neurodevelopmental and neurodegenerative effects of the fragile X premutation in both children and adults. This grant will correlate FMRP and other molecular measures with anthropometric, IQ and behavioral measures in families with FXS. It will also investigate the features of premutation carriers of fragile X syndrome.*

Co-Principal Investigator: Fragile X Research Center, NICHD, 7/1/08 to 6/30/13, \$464,433 annual direct. *This is a multi-center grant through the Mental Retardation Center in Seattle, Washington. The UC Davis portion of the project will involve a Patient Recruitment and*

Evaluation core, and an Administrative core. The patients seen through this center have FXS. This center will allow us to contact family members with the premutation to evaluate with the current proposal.

Co-Principal Investigator Overall Project, Principal Investigator UC Davis Project: AT Enhancement of Written Expression in Individuals with Neurodevelopmental Disorders, Coleman Institute, 11/01/04 to 10/31/09, \$51,731 annual direct. This project will assess the use of computer software in the written expression abilities of young individuals with neurodevelopmental disorders.

Co-Investigator: Fragile X-associated Tremor/Ataxia Syndrome, NIA, 06/15/05 to 05/31/11, \$265,297 annual direct. The principal objective of the proposed research is the identification of the mechanistic basis for a progressive neurological disorder, fragile X-associated tremor/ataxia syndrome (FXTAS), which involves intention tremor, gait ataxia, and dementia, and affects at least one-third of males over fifty years of age who carry small (premutation, CGG-repeat) expansions of the fragile X mental retardation 1 (FMR1) gene. This study covers the basic research on FXTAS and not the evaluation of patients so it will enhance our studies on FXTAS but it does not directly overlap with the current proposal.

Co-Investigator: Limbic Function in Carriers of the Fragile X Premutation, NIMH, 06/1/07 to 03/31/12, \$212,500 annual direct. This project investigates relations between molecular genetic, neuropsychological and physiological systems underlying social-emotional and memory functioning in adult males (18-45 years) with the fragile X premutation.

Co-Investigator: Visual Processing and Later Cognitive Effects in Infants with fragile X Syndrome, NICHD, 09/1/07 to 08/31/12, \$200,000 annual direct. This project investigates relations between early visual processing and later cognitive development in infants with the fragile X full mutation.

Principal Investigator: Ganaxolone Treatment of Fragile X Syndrome, UC Davis M.I.N.D. Institute Pilot Research Grant, 08/1/07 to 07/31/08, \$48,224 annual direct. This is a double-blind controlled trial of ganaxolone, a GABA_A receptor allosteric modulator or agonist, in children and adults with fragile X syndrome to assess improvements in behavior with a focus on anxiety and improvements in seizures.

Co-Principal Investigator: NeuroTherapeutics Research Consortium (1 of 6), NIDCR, 09/30/07 to 06/30/12, \$531,011 annual direct. The principal objective of the Research Consortium is implementation of a highly integrated, interdisciplinary approach to develop targeted molecular therapeutics for neurogenetic disorders, using the late-onset neurodegenerative disorder fragile X-associated tremor/ataxia syndrome (FXTAS) as its principal research paradigm. The fundamental challenge addressed by the Consortium is how to develop and integrate the various components required to achieve (and measure) a targeted therapeutic response to a CNS disorder.

Principal Investigator: Characterization and treatment of CNS abnormalities in premutation carriers (4 of 6), NIA, 09/30/07 to 06/30/12, \$704,415 annual direct. The overall goal of this project is to develop and utilize quantitative measures of CNS dysfunction in premutation carriers as outcome measures for targeted treatment studies of FXTAS.

Co-Investigator: Expression of the Fragile X Gene, NICHD, 12/01/06 to 11/30/10, \$212,500 annual direct. This is a competing continuation of the original grant. This project is designed to

examine the mechanisms underlying both the silencing of the FMR1 gene and the increase in FMR1 mRNA observed for carriers of premutation FMR1 alleles.

Co-Principal Investigator Overall Project, Principal Investigator UC Davis Project: Social-Affective Bases of Word Learning in Fragile X Syndrome and Autism, NIH, 03/8/08 to 02/28/13, \$183,749 annual direct. The overall focus of this UC Davis and University of Wisconsin Waisman Institute collaboration is the study of the behavioral and cognitive phenotype of fragile X syndrome (FXS) with autism and to investigate the neurological and molecular basis of this phenotype.

Principal Investigator: An Open Label Exploratory Study to Investigate the Effect of Fenobam Monohydrate (Fenobam 50 mg – 150 mg single dose) on Prepulse Inhibition Tests and Continuous Performance Tasks, in Adults with Fragile X Syndrome. Neuropharm, Ltd., 01/01/08 to 01/01/09, \$53,835 annual direct. This study is investigating the use of fenobam in pediatric adults with fragile X syndrome. This study is a phase I, open label study that is industry funded through Neuropharm, Ltd.

Co-Director: UC Davis Center of Excellence in Development Disabilities, DHHS Administration for Children and Families, 07/01/06 to 06/30/11, \$500,000 annual direct. The M.I.N.D. proposal is a synergistic collaboration between six centers with a comprehensive plan to increase capacity for interdisciplinary training, intervention, community services and advocacy in Northern California for individuals with developmental disabilities and their families. Goals and activities include education, early intervention, assistive technology and health.

Co-Principal Investigator: Fragile X Research and Newborn Screening, NICHD, 07/01/08 to 06/30/13, \$464,433 annual direct Davis component. This is a multi-center grant through the Mental Retardation Center in Seattle, Washington. The UC Davis portion of the project will involve newborn screening for fragile X, a Patient Recruitment and Evaluation core, and an Administrative core. This center will allow us to contact family members with the premutation to evaluate with the current proposal. There is no significant overlap with current proposal.

Community Service

ReachMD radio X-M157 media presentation on fragile X disorders and their treatment, August 11, 2008.

Board Member of the National Fragile X Foundation, 1997 to present.

Member of the Scientific and Clinical Advisory Committee of the National Fragile X Foundation, 2002 to present.

Awards and Honors

Lifetime Achievement Award given by the National Fragile X Foundation, July 2008