

Mental Retardation and Developmental Disabilities (MRDD) Branch NICHD



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EXECUTIVE SUMMARY

This document is the quadrennial report of the Mental Retardation and Developmental Disabilities (MRDD) Branch to the National Advisory Child Health and Human Development (NACHHD) Council. The MRDD Branch is a vital, evolving entity within the Center for Developmental Biology and Perinatal Medicine (CDBPM) at the National Institute of Child Health and Human Development (NICHD). The MRDD Branch provides the NICHD with a focus for research and research training aimed at understanding, preventing, and ameliorating MRDD* and related conditions.

The Branch's research portfolio includes studies on etiology, pathophysiology, screening, prevention, treatment, and epidemiology. The Branch research falls into five major categories: Center programs supported by the MRDD Branch; biomedical, genetic/genomic research, and chromosome abnormalities; biochemical and metabolic research; behavioral and biobehavioral research; and newborn screening and prenatal screening and diagnosis.

During the last four years, the Branch has consistently supported between 490 and 500 grants and their component projects (see [Table 1](#)). The Branch has also issued requests for applications (RFAs) and program announcements (PAs, PARs, PASSs), either alone or cooperatively with other Institutes (see [Appendix C](#)). Further, the Branch has organized and conducted meetings (see [Appendix F](#)), sponsored and encouraged new young investigators as grantees, and expanded the Centers Program, which continues to flourish.

In addition to providing a summary of the Branch's activities and accomplishments over the last four years, this report includes an enhanced discussion of possible future directions for the Branch over the next four years. The enhanced future directions represent an ongoing commitment by the NICHD leadership to seek outside input into the Institute's planning process and to keep the process transparent.

MRDD RESEARCH CENTERS (MRDDRCs) AND OTHER BRANCH CENTER PROGRAMS

The Branch continues to fund the congressionally mandated MRDDRCs Program, which focus on providing MRDD investigators with core facilities and services that support a broad array of research efforts. The Centers have been highly successful in unraveling many of the causes of MRDDs. However, successful interventions are still lacking or insufficient for most conditions. The NICHD's goal for the Program is to have the Centers begin to facilitate multi-site clinical trials within the next five years.

* The MRDD Branch and the NICHD embrace the concept of using alternatives to the term "mental retardation"; but, as does the American Association on Intellectual Disabilities, the Branch "acknowledges that this term will continue to have relevance in the diagnostic, legal, and public policy arenas." Throughout the United States, several other terms are in common use, including cognitive developmental disability, cognitive impairment, developmental disability, and intellectual disability. Because professionals and laypersons use the terms interchangeably and use no term consistently, this report uses MRDD throughout.

In addition, the Branch created the “Centers-within-Centers” concept by arranging for other Centers to use the resources of the MRDDRCs’ cores. These cores provide access to research tools and patients, as well as advice on developing research protocols and establishing databases. Initially, the “Centers-within-Centers” concept was applied to the Fragile X Syndrome Research Centers (FXSRCs) Program; currently, though, the Rare Disease Cooperative Research Centers (RDCRCs) Program also uses the services of these research cores.

The Branch’s support for the Collaborative Programs of Excellence in Autism (CPEAs) continues to reap fruitful results. The CPEAs have collected and examined the DNA from 300 multiplex families (those with more than one member with autism)—the largest existing sample for which extensive phenotype and genotype measures are known for all family members. The NICHD, through the MRDD Branch, also supports the Studies to Advance Autism Research and Treatment (STAART) Network, which is led by the National Institute of Mental Health (NIMH).

Since its last report to the NACHHD Council, the Branch has also started supporting one of the Senator Paul Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRCs), a project led and managed by the National Institute on Arthritis and Musculoskeletal and Skin Disorders (NIAMS). NICHD funding of a second center is expected to begin soon.

BIOMEDICAL, GENETIC/GENOMIC, AND CHROMOSOMAL ABNORMALITIES RESEARCH

This research area has long been at the heart of the Branch’s research portfolio. Efforts to understand Down syndrome, Prader-Willi syndrome (PWS), Angelman syndrome (AS), Rett syndrome, Fragile X syndrome, and other conditions account for a great deal of the Branch’s resources, both within the Centers Programs, and for individual projects. Although this research continues to elucidate aspects of these conditions, methods of treating or ameliorating many of these conditions and their developmental and health consequences remain elusive.

Research on Down syndrome now begins in infants, and continues through to the “oldest old” subjects—those older than 60 years. This lifespan approach to the condition has led to a variety of findings. For instance, using mouse models made available by the NICHD, researchers are selectively eliminating certain genes to study the contributions of those genes to the overall phenotype of Down syndrome. These studies may reveal ways to create interventions that target specific gene pathways to better treat aspects of the syndrome.

Work also continues on understanding dementia in those with Down syndrome. Individuals with Down syndrome, who are older than 30 years, show neuropathological features of Alzheimer disease, although the location and distribution of these features are more variable than in traditional Alzheimer disease. Imaging studies have pinpointed a potential focus for the dementia’s origin; hippocampal glucose activity decreases in individuals with Down syndrome, both as they age, and as they progress toward dementia. Activity also decreases in the posterior cingulate, part of the limbic circuit affected in those with Down syndrome who develop Alzheimer disease, and in normal controls who develop the condition. These findings may also shed light on the mechanisms of Alzheimer disease and could provide avenues for possible prevention and treatment in persons who do not have Down syndrome.

BIOCHEMICAL AND METABOLIC RESEARCH

The NICHD, through the MRDD Branch has long supported research on phenylketonuria (PKU), a metabolic disorder that, if untreated, can cause mental retardation. During the reporting period, the NICHD completed the Maternal PKU Collaborative Study, the largest and most definitive clinical study of maternal PKU to date. The 18-year prospective study included more than 120 clinics in five countries using a uniform research protocol. The findings, published in *Pediatrics* in 2003, clearly demonstrated that restricting phenylalanine in the diets of women with clinically significant hyperphenylalanemia beginning before or early in, and continuing during pregnancy decreased the incidence of intellectual disability, microencephaly, congenital heart disease, and intrauterine growth retardation in their offspring. The study and findings provide a knowledge base that far exceeds the initial goals of the effort. For instance, as the number of women of reproductive age with PKU continues to grow, it is critical to monitor the nutritional status of this high risk population and to ensure appropriate metabolic management.

Using mice with multiple deficiencies in glutaryl-CoA dehydrogenase (GCDH), an enzyme involved in lysine and tryptophan synthesis, researchers are learning about glutaric acidemias, a sometimes fatal disorder that arises from deficiencies in GCDH and can cause mental retardation. Multiple-GCDH deficiency during pregnancy correlates with elevated alpha-fetoprotein concentrations in serum and amniotic fluid, as well as with cystic renal disease and fetal growth delay. These findings may identify markers for these diseases that are detectable early in pregnancy, allowing for health care providers to better counsel and manage women at risk for these problems.

BEHAVIORAL AND BIOBEHAVIORAL RESEARCH

Simultaneous to studying the origins and mechanisms of various MRDD conditions, the Branch also supports research on the behavioral and biobehavioral aspects of these conditions. Much research during this reporting period focused on autism and autism spectrum disorders (ASDs), therefore the Branch has opted to highlight some of the findings of ASD research in this report.

The NICHD continues to be an active member of the congressionally-mandated NIH Autism Coordinating Committee and the Interagency Autism Coordinating Committee. The NIH recently initiated development of a new Centers Program, *Autism Centers of Excellence (ACE)* to better coordinate the substantial array of NIH-sponsored autism research projects efforts. This new initiative encourages applications from investigators currently in the CPEA Network and STAART Centers, as well as others who believe that they have sufficient expertise and resources to coordinate and implement a center or multi-site research program. NIH leaders are looking to the ACE program to centralize, coordinate, and standardize autism databases and develop improved intervention partnership with other NIH Institutes. The MRDD Branch is poised to take a lead role in this initiative.

Branch staff, in cooperation with other Institutes' program officers, have also facilitated the formation of the *Baby Sibs Consortium*, a research group studying the infant siblings of children diagnosed with autism or ASDs. This affiliated group of 11 investigators includes some members of the CPEA Network, as well as members of the STAART Centers. The

Consortium's efforts have established an operational framework for investigating the earliest features, which possibly represent warning signs and deserve monitoring and early intervention. These studies have already provided results that have led to testing of hypotheses about the earliest signs of autism and have formed the basis for further studies.

NEWBORN SCREENING AND PRENATAL SCREENING AND DIAGNOSIS

The NICHD is identifying goals and proposed programs for the Newborn Screening Research Initiative (NSRI) in areas of research that further the Institute's mission to prevent MRDD. Not only is the MRDD Branch supporting design and development of new and innovative screening assays and treatments, but it has also initiated studies of the implications and consequences of newborn screening. Branch support also focuses on developing large-scale data-sharing processes and other infrastructure resources that will facilitate clinical trials, reporting and tracking guidelines, and computer algorithms that process data based on quantified disease-specific analyte patterns. The Branch will continue to support a workgroup of newborn screening specialists that is providing recommendations on when to test and what conditions to include.

At the same time, the Branch provides a focus for the NICHD's support of improving existing prenatal diagnostic measures, including chorionic villus sampling (CVS), amniocentesis, and ultrasound. The Institute is also committed to developing non-invasive, safe, relatively inexpensive, and accurate techniques for prenatal screening, such as the First and Second Trimester Evaluation of Aneuploidy Risk (FASTER) trial, with support through the MRDD Branch.

In addition to these five areas of research emphasis, the MRDD Branch also continues to support research studies that focus on as many as 80 different rare diseases or clinical syndromes (see [Appendix H](#)), as well as research into assistive devices and technologies to improve the lives of those affected by MRDD from infancy through old age.

BRANCH FUTURE DIRECTIONS

The MRDD Branch was the first NICHD component to employ a new process for preparing its future directions. This process included the assembly of an expert panel. The panel reviewed the Branch's portfolio and supported efforts to identify and to provide guidance on possible strategic directions and priorities for future Branch research support initiatives or strategic emphasis.

The expert panel included scientists, advocates, members of the public, and two liaisons to the NACHHD Council to participate in an analysis of their research portfolio. Branch staff considered the panel's recommendations in developing and informing the *Future Directions for the MRDD Branch* section of this report.

Although the process will continue to evolve as other Branches complete the enterprise, the NICHD believes that such input will broaden and enhance the Institute's planning process and provide new ideas for addressing ever-changing research needs.

A number of overarching themes emerged from the expert panel's discussions, among them:

- Panel members believed that the Branch should continue to emphasize the NICHD's ongoing overall strategic planning theme *From Cells to Selves* in its report and in its research portfolio.
- The panel indicated that, informally, the Branch's portfolio embodied the idea that MRDD conditions are lifespan issues, but believed that the Branch should formalize this concept into its research priorities.
- Panel members noted the commonalities among MRDD conditions and suggested that a focus on these common aspects could be a way of accelerating significant advances in the field. These commonalities also suggest areas for strategic partnerships and collaborations.

Branch staff also identified specific future directions within its major areas of scientific emphasis. For instance, the fifth year hiatus in the competition cycle for the MRDDRCs occurs in 2007. This pause provides an opportune time to contemplate changes for the Centers that may include greater sharing of resources, collaboration among users, and opportunities for translation of knowledge about the causes of MRDD into interventions.

In its support of autism research, the Branch will lead in the design and implementation of the NIH ACE program, to foster efficient use of resources and collaborations among a larger number of investigators in autism research. The program will encourage applications that involve multi-site projects with specific research foci. The research may also include collaborative studies and data-sharing from exemplar scientists in a specific field who, together, can contribute to the field in ways each could not individually.

To further the goals of the NSRI, the MRDD Branch supports and sponsors development of the scientific and medical evidence underpinning recommendations that arise from the newborn screening specialists working group. These recommendations include identifying the conditions for which to screen, both across the country and internationally, and determining methods and protocols to test for the conditions. The MRDD Branch will continue to foster research into the natural history of specific genetic conditions, as well as the ethical, legal, and social issues (ELSI) that surround newborn screening on a national scale.

Another area of possible future activity for the Branch is involvement in trans-NIH multidisciplinary research agendas to study the various biomedical, clinical, social, cultural, familial, and personal issues surrounding MRDDs across the life continuum. The MRDD Branch will continue to participate actively in trans-NIH working groups that address ataxia-telangiectasia, epilepsy, amyloidoses, tuberous sclerosis, and neurofibromatosis, as well as those involved in neuroinformatics/neuroscience, autism, rare diseases, muscular dystrophy, gene therapy, and interdisciplinary research and training.

The following sections highlight some of the more interesting or high impact research and research findings supported by the MRDD Branch. Although these descriptions are by no means

comprehensive, they provide a useful overview of Branch activities for fiscal year 2001 through fiscal year 2005. Further information on future research directions for the MRDD Branch is outlined in the *Future Directions for the MRDD Branch* section of the report.

THE EVOLUTION OF THE CENTERS PROGRAM

Congressional mandate originated the MRDD* Research Centers (MRDDRCs) Program, the flagship program of the NICHD, one year after the founding of the NICHD in the early 1960s. The Centers Program grew significantly during this reporting period to include congressionally mandated FXSRCs “Centers-within-Centers” and two RDCRCs, all of which access core services that the MRDDRCs provide. In addition, the MRDD Branch is responsible for one site in the Muscular Dystrophy Cooperative Research Centers (MDCRCs) Program, a congressionally mandated effort that began in 2003. Further, while the CPEA Network continues to thrive, the STAART Centers Program, initiated in response to the *Children’s Health Act of 2000*, now adds to the Branch portfolio in autism research.

THE MRDDRCs PROGRAM

The MRDDRC Program currently consists of 14 Centers located at universities and children’s hospitals throughout the country (see [Appendix A](#)). A P30 core grant mechanism funds infrastructure in the form of cores that support independently funded, MRDD-relevant projects and New Program Development Projects. New Program Development Projects represent a small portion of the overall budget expenditure within an individual Center. Similarly, while other Centers that access MRDDRCs have some unique cores, they use existing affiliate MRDDRC cores extensively. Center directors and administrators meet to integrate the MRDDRCs into a network; this network interacts directly with the NICHD director, the director of the CDBPM, and the MRDD Branch staff. The meetings include a scientific symposium and a gathering of the editorial board of *Mental Retardation and Developmental Disability Research Reviews*, the official journal of the Society of Developmental Pediatrics. Although this publication associates with the MRDDRCs, its funding is independent.

The Centers differ in many aspects, including (but not limited to) their scientific focus, size, lifespan, and history. Although these differences impart a unique quality to and environment for each Center, the MRDDRCs share some common features that are discernible and important:

- Each Center presently supports at least 40 to more than 100 projects, and at least 20 to more than 70 principal investigators (hereafter called “affiliates”), who receive funding from

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numerous NIH Institutes and Centers, other federal agencies, and foundations within the private sector, allowing the Centers to support substantially more projects and affiliates than would be possible using NICHD support alone.

- The MRDDRCs increasingly leverage resources from their environment (e.g., host institutions, private donors, etc.) to facilitate growth, which stimulates MRDD research far in excess of the NICHD's investment and makes the Institute's contribution very cost-effective.
- The MRDDRCs continue to increase the quality and diversity of the services that they provide. Information technology and bioinformatics and biostatistics services support gene array, proteomics, and behavioral and clinical core services. Translational and clinical research projects now comprise almost half of all projects for a growing minority of Centers, particularly those that competed successfully in 2004. The Centers now actively pioneer new technologies and instrument development that represent unique, evolving resources.

2007, which is the fifth-year hiatus in the competition of the MRDDRCs, will provide program staff the opportunity to update program guidelines and issue new guidelines that reflect new program goals. As more investigators accessing the Centers receive their funding from other Institutes, government agencies, and foundations, program staff will reach out to other agencies and enlist them as partners to enhance funding of the MRDDRCs. Such partnering and outreach enables expansion of core services at some Centers, facilitates sharing of unique resources among investigators at various MRDDRCs and collaboration among users, and stimulates translation of knowledge about the causes of MRDD to interventions. Such partnering also permits the MRDDRCs to better stimulate translation, enabling them to adapt and adopt infrastructure necessary for maintaining and linking databases for the collection and sharing of information, thus enhancing the power of studying specific populations.

Growth of the Program

The need for affiliates from one Center to access unique core facilities at another Center encourages the integration of the MRDDRCs into a network. Although the word “network” has been in the MRDDRC guidelines for some time, it was more of a concept than a principle, until affiliates fostered more purposeful collaborations among themselves over the past eight years. As mentioned, MRDD Branch staff fostered the concept of “Centers-within-Centers” and developed other Centers programs as trans-NIH projects. The MRDDRCs and other Programs now mutually enrich each others' own resources and cores. The new Centers and collaborative projects link the MRDDRCs into a nascent network (see [Figure 1](#), [Figure 2](#), and [Appendix A](#)), which now serves as a multidisciplinary networking prototype exemplar that the NIH Roadmap Initiative seeks to establish.

The precise impact of the MRDDRC Program and its nascent network on the MRDD field is immeasurable. However, tracking the impact factor for *Mental Retardation and Developmental Disabilities Research Reviews* can provide a glimpse of how the field as a whole is doing (see [Table 2](#)); the *Reviews* impact factor rose from 1.442 in 2001, to 2.254 in 2002, to 3.479 in 2003. Most striking is the ranking of the *Reviews* among the clinical neurology, neuroscience, pediatrics, and psychiatry journals over the past five years. Among clinical neurology journals, *Reviews* rose from 89th out of 132 in 1999, to 15th out of 135 in 2003. Among pediatrics journals, its rank rose from 36th out of 72 in 1999, to 3rd out of 168 in 2003, a remarkable increase in importance in the clinical community at large.

FRAGILE X SYNDROME (FXS) RESEARCH CENTERS (FXSRCs): **“CENTERS-WITHIN-CENTERS”**

The FXSRC Program connects with the existing MRDDRC Program to support research that would improve the diagnosis and treatment of, and find a cure for FXS. MRDD Branch staff developed this initiative, primarily in response to the *Children’s Health Act of 2000* (P.L. 106-310), which directed the NICHD to “...expand, intensify and coordinate the activities of the Institute with respect to research on the disease known as Fragile X.” The Act provided for the establishment of at least three FXSRCs to conduct and support basic and biomedical research into the detection and treatment of FXS.

These “Centers-within-Centers” stimulate research relevant to FXS by encouraging studies of developmental neurobiology, pathophysiology, genetics, proteomics, epidemiology, structure-function correlations, clinical populations, and behavior and biobehavior. The NICHD FXSRCs are a national resource that fosters communication, innovation, and high-quality research in FXS, and that provides a stimulating, multidisciplinary environment to attract both established and new investigators. The Centers, their affiliates, and a description of their research appear below. For a map of the Center locations and their affiliate sites, see [Figure 2](#).

Baylor College of Medicine (Houston, Texas)

AFFILIATED SITE AT EMORY UNIVERSITY (ATLANTA, GEORGIA)

This FXSRC has three projects and one core dedicated to FXS research. The projects use a comprehensive test battery administered, if needed, in a mobile laboratory, to assess Fragile X Tremor/Ataxia Syndrome (FXTAS) among premutation carriers; elucidate mechanism(s) of neurodegeneration associated with premutation status using organisms created with ribocytosine-guanine-guanine (CGG) repeats; and focus on understanding the basis of anxiety observed in full-mutation individuals with FXS and in some premutation individuals who exhibit high mRNA levels. A neurophysiology core utilizes the hippocampal slice preparation to assess both “baseline” physiological transmission and short- and long-term synaptic plasticity in this critical region of the central nervous system.

University of Washington (Seattle, Washington)

AFFILIATED SITE AT UNIVERSITY OF CALIFORNIA AT DAVIS (DAVIS, CALIFORNIA)

This FXSRC correlates molecular and clinical data to better understand the predictive value of molecular parameters and their possible clinical relevance to FXS. The projects focus on why transcription of *Fragile X Mental Retardation 1 (FMR1)* gene occurs in males with expanded CGG repeats and a hypermethylated *FMR1* promoter (known as a full mutation), studies replication timing for *FMR1* in premutation males as a way to account for the observed high levels of mRNA, and uses a methylation-sensitive chromatin-immunoprecipitation (ChIP) method to analyze chromatin modifications in fully, partially, or unmethylated *FMR1* alleles. The clinical cores conduct genetic, neuropsychological, and medical assessments of all individuals in the studies and determine the mRNA levels of identified premutation carriers.

University of North Carolina (Chapel Hill, North Carolina)

AFFILIATED SITE AT UNIVERSITY OF KANSAS (KANSAS CITY AND LAWRENCE, KANSAS)

This FXSRC studies family adaptation to FXS in an integrated, longitudinal study of 100 families whose data each of this Center's projects share. The projects include: *Parent and Family Well-being in FXS*, exploring the extent to which mothers and fathers of children with FXS experience a positive quality of life, have hope about the future, and are protected from or experience adverse mental health outcomes, such as depression, anxiety, anger, and stress; *Maternal Responsivity and the Development of Children with FXS*, examining the extent to which parents construct environments and engage in behavior that promotes cognitive, language, academic, and adaptive skills for their children with FXS; and *Family Adaptation to Temperament and Challenging Behavior in FXS*, exploring how families respond to a wide array of their children's challenging problems—although these behaviors have a biological basis, parents play important roles in the extent to which children express and regulate the behaviors.

RARE DISEASE COOPERATIVE RESEARCH CENTERS (RDCRCs)

An estimated 6,000 rare diseases or conditions affect approximately 25 million people¹ in the United States. In November 2002, the *Rare Disease Act of 2002* (P.L. 107-280) directed the NIH Office of Rare Diseases to establish a *Rare Disease Clinical Research Network*—a collaborative and coordinated network of investigators and patient groups that investigates rare diseases in partnership with technology leaders to enhance communication and resource sharing via a multidisciplinary approach. The Network collects clinical information to develop biomarkers and new approaches to diagnosis, prevention, and treatment; provides content for an Internet-based resource site about rare diseases; and trains new clinical investigators in rare disease research. The Network also supports a comprehensive and integrated approach to data collection, storage, and management and integrates clinical data with other unique data, including genetic, imaging, pathologic, and laboratory data through the Data and Technology Coordinating Center.

The first competition for the RDCRCs in 2003 established eight funded centers; there are now 10 (see [Figure 1](#)). Through the MRDD Branch, the NICHD provides scientific management for the following two Centers and their affiliate sites.

Children's National Medical Center (Washington, D.C.)

AFFILIATED SITES AT: BAYLOR COLLEGE OF MEDICINE (HOUSTON, TEXAS); CHILDREN'S HOSPITAL OF PHILADELPHIA (PHILADELPHIA, PENNSYLVANIA); YALE UNIVERSITY (NEW HAVEN, CONNECTICUT); GEORGETOWN UNIVERSITY (WASHINGTON, D.C.); UNIVERSITY OF CALIFORNIA AT LOS ANGELES (LOS ANGELES, CALIFORNIA); VANDERBILT UNIVERSITY (NASHVILLE, TENNESSEE); AND MOUNT SINAI SCHOOL OF MEDICINE (NEW YORK CITY, NEW YORK)

This RDCRC is a highly integrated network of investigators with a long history of cooperative interactions. With a focus on urea-cycle disorders, the investigators have established a registry to estimate incidence and prevalence of the eight urea-cycle disorders they study.

In general, this RDCRC:

¹ NIH Office of Rare Diseases; http://rarediseases.info.nih.gov/html/resources/about_ord.html.

- Performs longitudinal natural history studies of urea-cycle disorders to understand morbidity, mortality, and treatment efficacy;
- Surveys and promotes newborn screening for urea-cycle disorders to aid in identification and treatment;
- Tests new approaches to therapy for these disorders to help bring new drugs to market in collaboration with pharmaceutical companies;
- Develops novel non-invasive methods for assessing changes in urea synthesis, both over time and under varying treatment conditions;
- Performs neuropsychological and neuroimaging studies on affected individuals identified at various sites to better understand the effects of hyperammonemia on neurocognitive function;
- Maintains a Web site, in collaboration with the Data and Technology Coordinating Center and the National Urea Cycle Disorders Foundation, to provide clinical and research information on urea-cycle disorders to the public, health care providers, and affected families; and
- Promotes the entrance of M.D. and Ph.D. investigators into the study of urea-cycle disorders through a postdoctoral fellowship training program.

Baylor College of Medicine (Houston, Texas)

AFFILIATED SITES AT: UNIVERSITY OF ALABAMA AT BIRMINGHAM (BIRMINGHAM, ALABAMA); UNIVERSITY OF FLORIDA (GAINESVILLE, FLORIDA); CHILDREN'S HOSPITAL (BOSTON, MASSACHUSETTS); GREENWOOD GENETICS CENTER (GREENWOOD, SOUTH CAROLINA); CHILDREN'S HOSPITAL (SAN DIEGO, CALIFORNIA); AND UNIVERSITY OF CALIFORNIA, IRVINE, MEDICAL CENTER (IRVINE, CALIFORNIA)

This RDCRC focuses on new therapies and new diagnostics and seeks to:

- Establish natural history protocols for three disorders: Rett syndrome, PWS and AS;
- Develop a new therapeutic trial for AS;
- Use microarray comparative genomic hybridization to search for deletions in patients with PWS-like features, or in those with early morbid obesity;
- Develop a new methodology for detecting large chromosomal deletions in individuals with Rett syndrome;
- Provide prenatal diagnosis of deletion cases of PWS and AS using chromosome microarray analysis; and
- Distinguish between class I and class II deletions for PWS and AS with two unique research microarrays.

NETWORK ON THE NEUROBIOLOGY AND GENETICS OF AUTISM: COLLABORATIVE PROGRAMS OF EXCELLENCE IN AUTISM (CPEAS)

The NICHD, in collaboration with the National Institute on Deafness and Other Communication Disorders (NIDCD), has supported the international Network on the Neurobiology and Genetics of Autism since 1997. The first investment was \$45 million for five years; more recently, the Branch invested \$60 million for another five years.

The current network of eight CPEAs and one affiliated program continues to conduct research to learn about the possible causes of autism, including genetic, immunological, and environmental factors, as well as diagnosis, early detection, behavioral and communications characteristics, and treatment of autism.

The CPEA Network was the first of its kind to address unique research topics at each center. Although each multidisciplinary, often multi-site project has a unique focus and research plan, many projects also use a common diagnostic protocol and common core measures, enabling the Network to investigate more far-reaching questions than a single project could address alone. In addition, whenever possible and necessary, multiple sites pool their data to address specific research questions. The CPEAs have linked scientists from the United States, Canada, Britain, and five other countries in the study of more than 2,000 families for nearly 10 years. As a result, the CPEAs have data on the genetic and phenotypic characteristics of the world's largest group of well-diagnosed persons with autism.

For the locations of the CPEAs and their affiliate sites, and descriptions of the CPEA projects, see [Appendix B](#). In addition, highlights of scientific advances made by CPEA investigators appear in the *Advances in Behavioral and Biobehavioral Research* section of this report.

Studies to Advance Autism Research and Treatment (STAART) Centers Program

The *Children's Health Act of 2000* (P.L. 106-310) mandated that the NIH support a new program of at least five centers of excellence focused on autism and related disorders. In response, the Institutes involved in the NIH Autism Coordinating Committee, including the NICHD, the NIMH, the NIDCD, the National Institute on Neurological Disorders and Stroke (NINDS), and the National Institute of Environmental Health Sciences initiated the STAART Centers, a five-year, \$65 million research effort focused exclusively on autism. Each STAART site supports and conducts both individual and collaborative projects to learn more about the causes, diagnosis, early detection, prevention, and treatments of autism. The NIMH leads the NIH Institutes' efforts on STAART, and the other Institutes in the NIH Autism Coordinating Committee also provide programmatic support. (For the locations of the STAART sites, see [Figure 3](#).)

In 2003, the CPEAs and STAART sites launched a Data Coordinating Center, which the NIMH and the NICHD fund jointly, to provide data management and statistical support, coordinate and facilitate communication among the researchers, and establish a common measures database for both networks.

THE SENATOR PAUL D. WELLSTONE MUSCULAR DYSTROPHY COOPERATIVE RESEARCH CENTERS (MDCRCs)

Collectively, muscular dystrophies have a high impact on health, affecting tens of thousands of people in the United States alone. Progressive weakness and wasting of muscles characterize the muscular dystrophies, and many cases of muscular dystrophy represent new occurrences of disease without prior family history. Despite advances in knowledge about the genetic defects of these diseases, the life expectancy and quality of life for children and adults with muscular dystrophy have not improved significantly. Researchers also need to learn more about

pathogenesis of the diseases to improve early detection and screening, diagnosis, treatment, and prevention.

NIAMS issued the *Muscular Dystrophy Cooperative Research Centers* RFA in 2003. The initiative was reissued in 2004 as the *Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers* (RFA-AR-04-008). The initiative combined the research efforts of multiple Institutes (including NIAMS, NINDS, and the NICHD) on all forms of muscular dystrophy to promote: side-by-side basic, translational, and clinical research; resources that the national muscle biology and neuromuscular research communities can use; and training and advice about muscle diseases for researchers and physicians who provide initial diagnosis and treatment, including rehabilitation, care for cognitive and behavioral concerns, and therapy for other system complications.

Each Center in the MDCRC Program, which operates under guidelines for NIH cooperative agreements, brings expertise, infrastructure, and resources that focus on major questions about muscular dystrophy. Centers use innovative research designs and state-of-the-art technologies; provide environments and core resources that enhance collaborations of established basic, clinical, and behavioral science investigators to study muscular dystrophy research questions; and promote cross-disciplinary research training.

In the first cycle of the MDCRC competition, which funded three Centers in 2003, the NICHD funded the MDCRC at the **University of Washington School of Medicine** (Seattle, Washington), with an affiliated site at Fred Hutchinson Cancer Research Center (also in Seattle). The MRDD Branch also supports the Scientific Management Center for this site and its affiliated site.

The University of Washington School of Medicine Wellstone MDCRC focuses on translational research aimed at finding treatments for the muscular dystrophies. Currently, the main disease targets are Duchenne muscular dystrophy (DMD), an X-linked disease that is the most common, affecting approximately one in 3,500² male births; and myotonic dystrophy (DM1), an autosomal-dominant form that is the most common³ form of adult-onset muscular dystrophy. The Center aims to identify mechanisms of muscle pathology in the dystrophies, and to exploit those findings to develop gene- and stem cell-based therapies. Studies begin in animal models to establish adequate safety and efficacy, and then continue into clinical trials.

In addition, the Center interacts with a core, supported by the Muscular Dystrophy Association, that provides clinical patient care to facilitate future patient participation in ongoing translational research and planned clinical trials of this and other MDCRCs.

² *Duchenne muscular dystrophy*. (2005). MedlinePlus Medical Encyclopedia, National Library of Medicine, NIH; A.D.A.M., Inc. <http://www.nlm.nih.gov/medlineplus/ency/article/000705.htm>, Retrieved May 31, 2005.

³ *Muscular dystrophy*. (2005). MedlinePlus Medical Encyclopedia, National Library of Medicine, NIH; A.D.A.M., Inc. <http://www.nlm.nih.gov/medlineplus/ency/article/001190.htm>, Retrieved May 31, 2005.

ADVANCES IN BIOMEDICAL AND GENETIC/GENOMIC RESEARCH— CHROMOSOME ABNORMALITIES

Cytogenetic abnormalities, which can include trisomy, mosaicism, or chromosome rearrangements, such as translocations, terminal deletions, interstitial deletions, or interstitial duplications cause approximately 20 percent⁴ of mental retardation. Chromosome abnormalities also account for a substantial amount of morbidity and mortality, especially among children. Recent advances in high-resolution cytogenetic analysis and the development of the molecular cytogenetics field, mainly through the application of fluorescence *in situ* hybridization (FISH), provide opportunities for identifying subtle chromosomal rearrangements, such as cryptic deletions, as the causes of a number of genetic syndromes. The following section highlights some findings of Branch-supported research on chromosome abnormalities.

PRADER-WILLI SYNDROME (PWS)

PWS is the most common⁵ known genetic cause of life-threatening obesity in children. Insatiable appetite, morbid obesity, temper tantrums, and outbursts of aggression characterize PWS. A long-sequence deletion of paternal genetic material on HSA15, or duplication of maternally expressed genes on HSA15 (in the absence of complementary paternal genetic material, a situation called maternal uniparental disomy) causes PWS. Two or more contiguous genes on maternal HSA15 are necessary to explain the complex set of behaviors and body composition found in classic PWS. These observations opened a new field of research on the phenotypic effects of imprinted genes of both paternal and maternal origin.

For many individuals with PWS, the intense preoccupation with food, lack of satiation, and food seeking are among the most striking characteristics of the syndrome. Concerns with food begin between ages one and six years and include persistent thoughts about food (ideation), food fixation, ritualistic eating, and unusual food behaviors and food preferences. Positron emission tomography studies show that individuals with PWS exhibit a brain activity pattern when hungry similar to that of normal individuals, but different brain activity patterns for satiety after food intake. Under specific caloric conditions, individuals with PWS can increase activation of the frontal cortical areas, a reaction that may represent changes in emotional state.

Persons with PWS exhibit maladaptive and compulsive behaviors; yet, such behaviors are very complex. Individuals with PWS who develop better adaptive skills can protect themselves from the emergence of problems later in life. Thus, interventions that build and promote adaptive skills become necessary and essential.

Individuals with PWS invariably have eating disorders, yet other behavioral disorders are not universal; individuals with uniparental disomy appear particularly at risk for psychotic illness in adult life. With respect to medications, some individuals with PWS respond well to selective

⁴ *Chromosomal Abnormalities*. (2005). March of Dimes Birth Defects Foundation. http://www.marchofdimes.com/professionals/681_1209.asp, Retrieved May 31, 2005.

⁵ Holm, V.A., Cassidy, S.B., Butler, M.G., Hanchett, J.M., Greenswag, L.R., Whitman, B.Y., & Greenberg, F. (1993). Prader-Willi syndrome: Consensus diagnostic criteria. *Pediatrics*, Feb;91(2), 398-402.

serotonin re-uptake inhibitors, while others do not. For more information about behavioral and biobehavioral research on PWS, refer to the *Advances in Behavioral and Biobehavioral Research* section of this report.

ANGELMAN SYNDROME (AS)

Although severe mental retardation, seizures, and an ataxic gait characterize AS, individuals with AS may also make repeated hand motions, occasionally display a strange fascination with water, and exhibit a lower threshold for smiling and laughter in social situations, leading to inappropriate laughter as a phenotypic characteristic. The prevalence of AS is approximately one in 15,000 to 20,000⁶ births. Deletion of the maternal copy of HSA15, as well as paternal uniparental disomy cause AS.

In 1997, researchers identified the genetic locus for AS, a mutation of *UBE3A*, the gene that encodes the enzyme E6-AP ubiquitin ligase. This mutation disables the enzyme that normally “tags” proteins fated for recycling within the cell. A few specific target proteins accumulate in the cell, leading to the clinical features of AS. In 1998, researchers created a mouse model for the defining molecular and neurological features of AS. AS mice also exhibit mis-regulation of calcium/calmodulin-dependent protein kinase II within the hippocampus, a feature that diminishes protein activity necessary to induce the cellular processes required for learning. Thus, a genetic defect that changes the enzyme E6-AP ubiquitin ligase indirectly alters the activity of calcium/calmodulin-dependent protein kinase II within the hippocampus, initiating a chain of molecular and cellular events that gives rise to a particular symptom of AS. This discovery has implications far beyond just AS for understanding the relationships between a single genetic change and a resulting complex phenotype.

WILLIAMS SYNDROME (WMS)

WMS, which has a prevalence⁷ of between one in 10,000 and one in 20,000, arises from deletions in a group of genes on the long arm of chromosome 7, including the *elastin* locus on 7q11. Cardiac, sensory, and cognitive defects, as well as distinctive facial features, abnormal calcium metabolism, failure to thrive during infancy, and moderate levels of mental retardation characterize many individuals with WMS. Molecular techniques establish the WMS diagnosis in 95 percent of cases.

Recent research has focused on *GTF2I* and *GTF3*, which encode members of the TFII-I family of transcription factors, and a relative, MusTRD1/BEN, which individuals with WMS abundantly express in the hippocampus. MusTRD1/BEN interacts with factors that modify proteins associated directly with chromatin and the nuclear matrix, thereby modifying the cell cycle. Study of individuals with WMS who have specific small deletions of the 7q11 region led researchers to focus on one region, which contains a member of the GFT2I/GFT2RD1 (BEN)

⁶ Williams, C. (2003). *How common is Angelman syndrome?* Angelman Syndrome Foundation, Inc. <http://www.angelman.org/angel/index.php?id=104>, Retrieved May 31, 2005.

⁷ American Academy of Pediatrics, Committee on Genetics. (2002). Policy Statement: Health care supervision for children with Williams syndrome. *Pediatrics*, Feb;109(2), 329.

family; these individuals exhibit specific variations in visual-spatial processing, social behavior, volume and structure of specific cortical regions (e.g., posterior parietal/occipital, superior temporal gyrus, and Sylvian fissure), and variations in ERP responses in spatial and auditory paradigms.

The major sources of variability in the cognitive and neural phenotypes of WMS depend on the parent of origin, which, coupled with atypical deletion size, result in specific differences in brain structures used for language and facial processing. For instance, the brains of individuals with WMS show increased activation to fearful faces, relative to happy or neutral faces. Sizes of specific areas in the brains of individuals with WMS predict electrophysiological responses; for example, enlargement of the temporal lobe, especially of the superior temporal gyrus and planum temporale, correlates with performance and verbal intelligence quotient (IQ). Further, the enlargement in related limbic areas (e.g., orbitofrontal cortex, parts of auditory thalamus, insula, cingulate, and amygdala) correlates with heightened response to encoding words with emotional content. Thus, neural circuitry predisposes those with WMS to processing and remembering language with emotional content, at the expense of the visual/spatial system.

Changes also occur at the cellular level, in those regions of the brain associated with the processing visual/spatial information. Cell size, process elaboration, and packing density and connectivity correlate directly with functional strength/impairment in the brains of individuals with WMS. Brains of those with WMS also lack the typical asymmetry of a normal brain, a situation that may underlie part of their behavior strengths, such as facility with using language and musicality.

DOWN SYNDROME

Down syndrome is a significant genetic cause of mental retardation in human populations, occurring in approximately one in 800 newborns, an incidence⁸ that has remained reasonably constant for the past century in virtually every ethnic group in the world. More than 95 percent of individuals with Down syndrome possess an extra copy of the smallest human chromosome, chromosome 21 (HSA21); 2 percent to 4 percent have partial trisomy, inherited from the balanced translocation of one part of HSA21 to another chromosome from one of the parents. In addition, 1 percent to 2 percent of individuals with Down syndrome are mosaic; they have both normal cells and trisomy 21 (Ts21) cells in their bodies.

Individuals born with Down syndrome today enjoy a greatly increased life expectancy compared with 25 years ago. Among Caucasian individuals with Down syndrome, life expectancy has tripled to approximately 70 years of age. Approximately 45 percent of individuals with Down syndrome survive past the age of 60, and about 15 percent live almost to the age of 70. The life expectancy of non-Caucasians with Down syndrome has risen in the same time frame, from younger than five years to nearly 35 years in Western cultures, although life expectancy is still significantly less than in the Caucasian population.

⁸ American Academy of Pediatrics, Committee on Genetics. (2001). Practice Guideline: Health care supervision for children with Down syndrome. *Pediatrics*, Feb;107(2), 442-449.

Genetics and Down Syndrome

In 2001, the tentative sequence of the long arm of HSA21 was estimated at about 225 genes; currently, HSA21 contains approximately 360 genes. With the identification of genes on HSA21, investigators now focus on commonalities among those genes to understand activities the genes might subserve, such as encoding channels, receptors, components of signaling pathways, transcription factors, or involvement in energy metabolism and utilization. On HSA21, 64 genes associate with nine such pathways, including MAP kinase, calcineurin signaling, mitochondrial functioning, RNA processing, and protein modification, to name a few.

Knowledge that such associations occur on a single chromosome is stimulating a new research direction in the study of pathways—instead of single genes—for making phenotype correlations. Investigators are moving away from a contiguous gene syndrome view, to a view of more cooperative or cascading gene syndromes, in which common features may arise from intersections in common functional pathways that converge.

Studies of mouse models, primarily partial trisomy models, focus most often on the Ts65Dn mouse, but also include Ts1Cje, Ms1Cje/Ts65Dn, Ts1Rhr, and Ms1Rhr mice. The Ms1Rhr/Ts65Dn mouse has proven to be a very important model because it is trisomic only for the region of HSA21 known as the Down Syndrome Critical Region. However, the phenotype of the Ms1Rhr/Ts65Dn mouse does not have the characteristics of Down syndrome, meaning that the region is neither obligate, nor critical, to the phenotypic features of Down syndrome in the mouse model system.

Clearly the partial trisomies have many of the characteristics exhibited by individuals with Down syndrome, and carefully designed behavioral experiments probe similarities that may exist among these mice groups. The partial trisomies also vary in their “clinical” presentations: mice with Ts1Cje, a smaller triplication, exhibit fewer symptoms than those with Ts65Dn. Ts65Dn mice have fewer Purkinje and granule cells in the cerebellum, while Ts1Cje have only fewer granule cells. The raphe nuclei contain fewer serotonergic neurons, but noradrenergic neuron numbers are normal in the locus coeruleus. In addition, basal forebrain cholinergic neuron reduction is less severe in Ts1Cje, as are the postnatal alterations in hippocampal function. Elective elimination of specific genes creates partial trisomic mice with two copies of specific genes, such as *App*, *Girk2*, and *Dyrk1*, enabling study of the contribution that specific genes make to the overall phenotype of Down syndrome.

Down Syndrome and Associated Conditions

Individuals with Down syndrome who survive into their third decade show the neuropathological characteristics of Alzheimer disease, although the location and distribution of these features are much more variable than in traditional Alzheimer disease. Imaging studies of elevated glucose metabolism in individuals with Down syndrome pinpoint the transentorhinal cortex as a potential focus for the origin of dementia in those with Alzheimer disease and in individuals with Down syndrome who develop Alzheimer disease. Those with lower, moderate Alzheimer disease exhibit increased hippocampal glucose activity; this activity actually decreases in individuals with Down syndrome, not only as they age, but also as they progress toward dementia. Further, activity decreases in the posterior cingulate, a part of the limbic circuit affected in individuals with Alzheimer disease and in individuals with Down syndrome who develop Alzheimer disease.

The “oldest old” subjects—those individuals with Down syndrome older than age 60, some now followed for the past quarter century, continue to inform and amaze. Although dementia is more frequent, full trisomy is less frequent in the older group. Slightly fewer members of the older group have the *APOE4* ϵ 4 allele, thought to be a predisposing variable for Alzheimer disease. Nonetheless, these individuals exhibit no unusual genetic rearrangements, nor do they exhibit an unusual pattern of over-expression of genes on HSA21.

Mouse models also provide potential therapeutic interventions and a better understanding of the molecular commonalities between Down syndrome and Alzheimer disease, including cholinergic deficits that arise from the basal forebrain. Neurons in the basal forebrain that innervate both the cerebral cortex and the hippocampus and depend on nerve growth factor (NGF) secreted and transported back to the basal forebrain to sustain this cholinergic neurotransmission. Studies of mouse models now clarify that the basal forebrain neurons do not die, as was long suspected, because direct infusion of NGF restores the secretion of acetylcholine. This process ceases at the synapses in the hippocampus because the axons cannot transport NGF back to their cell bodies in the basal forebrain. Tau, a protein normally associated with the microtubules of these neurons, is abnormally hyperphosphorylated because an HSA21 gene product, the amyloid precursor protein (APP) A β , accumulates over the first six months of life in the basal forebrain neurons of Ts65Dn mice. This accumulation slows transport of NGF to such a degree that the cholinergic neurons become functionally “dormant.” Because *App* is not triplicated in Ts1Cje mice, NGF transport and cholinergic function continue, resulting in more functional innervation.

OTHER MENTAL RETARDATION CONDITIONS

The MRDD Branch supports research on other conditions that are characterized by mental retardation. Some highlights from this research include the following:

- **Cornelia de Lange Syndrome (CdLS)** is a congenital multi-system disorder marked by facial abnormalities, upper limb defects, hirsutism, gastrointestinal defects, cognitive delays, and retarded growth. The prevalence⁹ of CdLS may be one in 10,000, but the phenotype varies, and clinical findings are the sole basis for the diagnosis. Although extremely rare, familial cases indicated the p13 region of chromosome 5 as a likely site for the CdLS gene. This minimal critical region contains 11 genes; but only one gene, which encodes for *Delangin* (*DLNG*; *NIPBL*), contains mutations that result in classic symptoms of CdLS. All mutations detected to date occurred *de novo*. In familial cases, no parent was affected, but all children in a family carried the same mutation, hinting at germ-line mosaicism as the mechanism. Further, individuals with milder phenotypes have missense or splice-site mutations; polymorphisms on the non-mutated allele can also modify the phenotype observed.

⁹ *Facts About Cornelia de Lange Syndrome*. (2005). Cornelia de Lange Syndrome USA Foundation, Inc. http://www.cdlsusa.org/about_cdls/faq.html, Retrieved May 31, 2005.

- **Smith-Magenis Syndrome (SMS)**, which is associated with deletions in the short arm of chromosome 17 (HSA17) in the p11.2 region, has a prevalence¹⁰ of one in 25,000. Persons with characteristic SMS have moderate mental retardation; speech and motor delays; behavioral abnormalities, including self-injurious behavior (SIB); insensitivity to pain; sleep disturbance; short stature and short fingers; and distinctive abnormalities of the head and face. Some may also be obese. SMS is one of the more common contiguous or cooperative deletion syndromes. The minimal critical region of HSA17 associated with SMS is about 950 kilobases, a region that contains approximately 25 genes. Some individuals with SMS have no overt deletions, but they do have novel deletions in *retinoic acid induced-1 (RAI1)*, resulting in a shortened RAI1, a protein normally localized in the nucleus. RAI1 resembles transcriptional co-activator TCF20 and may stimulate transcription by interacting with DNA-binding proteins. In neurons, RAI1 may stimulate the activation of other genes essential for proper neuron development. Having only one copy (called haploinsufficiency) of *RAI1* probably causes the behavioral, neurological, otolaryngological, and craniofacial aspects of SMS. However, the more variable phenotypic forms of SMS, such as heart and kidney defects, probably result from haploinsufficiency of other genes in the 17p11.2 critical region.

X CHROMOSOME DISORDERS

“X chromosome disorders” refers to a class of genetic syndromes associated with either mutations of genes located on the X chromosome, or an abnormality in the structure of the X chromosome that result in mental retardation. Conditions that fall into this category include X-linked adrenoleukodystrophy, Rett syndrome, FXS, and many others. The following section highlights MRDD Branch-funded research on two X chromosome disorders: Rett syndrome and FXS.

Rett Syndrome

Rett syndrome¹¹ is a devastating X-linked neurodevelopmental disorder that almost exclusively affects girls, making it one of the leading causes of intellectual disability and autism in females. Some 96 percent of girls with Rett syndrome have mutations in the *Methyl Cytosine-binding Protein 2 (MECP2)* gene on Xq28; the gene encodes MeCP2, a transcriptional repressor that binds methylated cytosines. Beginning between six and 18 months of age, these girls lose purposeful hand movements and speech; develop balance and coordination abnormalities; and experience decelerated head growth, tremors, seizures, stereotypies (including characteristic hand wringing), and hypoactivity. They also show anxiety and social behavioral abnormalities, such as gaze aversion and features of ASDs. Despite earlier theories that onset of symptoms typically began at around six months of age, careful analysis of videotapes from birth revealed that the early development of girls with Rett syndrome is not actually normal, suggesting the need for newborn screening and early intervention. Prenatal diagnosis also proves valuable for families in which germ-line mosaicism occurs.

¹⁰ Smith, A., et al. (Updated 15 March 2004). *Smith-Magenis Syndrome [del(17)(p11.2)]*. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2005. Available at <http://www.genetests.org>. Accessed 05/31/2005.

¹¹ Weaving, L.S., et al. (2005). Rett syndrome: Clinical review and genetic update. *Journal of Medical Genetics*, 42, 1-7.

Differences in the mutation pattern (e.g., truncation, missense, nonsense, C-terminal) prove to be important in the extent of the phenotype. Individuals who lack the characteristic *MeCP2* mutations may produce a truncated MeCP2, while those individuals with other truncating mutations led researchers to identify a second isoform, MeCP2B, which is most commonly expressed in the nervous system. Individuals who express the MeCP2 isoform variant exhibit a milder phenotype that includes some preservation of eye contact. Currently, sequence analysis/deletion analysis, or reanalysis of individuals with multiplex ligation-probe amplification enables investigators to identify 95 percent of affected individuals.

The phenotypic consequences of *MeCP2* mutations range from classic Rett syndrome, in those with random X chromosome inactivation (XCI), to mild or even no intellectual disability in girls with favorable XCI. Impaired *MeCP2* function may lead to mis-expression of genes crucial for neuronal development that mediates Rett syndrome pathogenesis, as well as some forms of autism and intellectual disability. Major disruptions of transcriptional silencing also occur in Rett syndrome, reducing levels of acetylated and methylated histones.

Males with *MeCP2* mutations do survive the perinatal period, although most experience severe early onset encephalopathy and die within the first year of life. Some male relatives may have non-syndromic neurologic problems of unknown etiology (1:6); others have learning disabilities, autism, and mild intellectual disability (1:20 to 1:50). Other known atypical variants of Rett syndrome include single base-pair deletions (806delG), which investigators found in a boy who manifested early onset encephalopathy. Novel frameshift mutations also occur in individuals who exhibit minimal change in head size and growth.

RETT SYNDROME AND OLFACTORY NEURONS

Some of the most interesting recent studies of Rett syndrome involve olfactory receptor neurons (ORNs), naturally regenerative neuroepithelium in the nasal mucosa that mediates the sense of smell and is readily accessible via biopsy. ORNs obtained from individuals with Rett syndrome contain a few dysmorphic mature ORNs, but many immature ORNs. Thus, ORNs from living individuals with Rett syndrome, like neurons from the brains of individuals with Rett syndrome obtained at autopsy, may undergo maturational arrest, which generally plateaus near the end of adolescence in girls with Rett syndrome.

Studies of normal development and temporal expression of *Mecp2* in mouse ORNs allowed correlation with neuronal maturity and functional synaptogenesis. In both neurons and glia, the regulation of signals that must cease for specific differentiation to initiate or end appears to be suspended in individuals with Rett syndrome.

Xenopus embryos are also useful models for studying Rett syndrome. When *Xenopus* embryos over-express the severe R168W-truncating mutation, they exhibit developmental defects, abnormal movement, and altered expression of pre-neural genes that result in excess numbers of neurons. Current studies focus on *Xenopus* embryos with constructs of different untranslated-region lengths and constructs transfected into various cell lines, enabling investigation of the functional consequences on RNA stability, protein translation, and subcellular localization, as well as on binding specific RNA-binding proteins.

ASSOCIATION BETWEEN RETT SYNDROME, PWS/AS, AND AUTISM

All individuals with Rett syndrome have significantly lower *MECP2* expression, regardless of whether they have overtly detectable *MECP2* mutations. Thus, it is likely that some of the genes that *MeCP2* should silence during development are not silenced; instead these genes remain transcriptionally active and make products that the cells secrete into the local “neighborhood.” Continued secretion, or too much secretion, creates an environment detrimental to the other cells and leads to some of the symptoms observed. These assumptions led to the “bad neighborhood” hypothesis in Rett mosaics—that is, that the effect of the Rett allele is not “cell autonomous.”

Some Branch-supported studies have focused on the known association between Rett syndrome, autism, and genes on Chromosome 15 (HSA15), particularly those in the region of the PWS/AS deletion, because defects in *MeCP2* expression occur in some individuals with autism and in those with AS and PWS. *MeCP2* deficiency affects the levels of expression of both *UBE3A*, the gene that encodes the enzyme E6-AP ubiquitin ligase, and the neighboring autism-associated gene that encodes a subunit of gamma-aminobutyric acid (GABA) receptor (R), *GABAR3*, without affecting imprinted expression. In fact, significant defects in *UBE3A/E6AP* expression occur in *Mecp2*-deficient mice and in individuals with Rett syndrome, AS, and autism. Homologous chromosome pairing occurs in the brains of those with autism and *MeCP2* binds to the DNA of these paired chromosomes. A methylated oligonucleotide decoy specifically blocks such *MeCP2* binding and decreases the percentage of paired alleles, bringing the association full circle.

SKILL STUDIES OF GIRLS WITH RETT SYNDROME

Scores on tests for temperament, atypical behaviors, and social interaction for girls with Rett syndrome are much worse than those of individuals with autism, as much as two standard deviations from the mean. Girls with Rett syndrome consistently exhibit abnormal adaptive/social-behaviors, SIBs, and self-isolation/ritualistic behaviors. Within studies of sensory profiles, girls with Rett syndrome scored very poorly on endurance/tone, inattention/distractibility, registration, social sensitivity, and fine motor/perceptual skills. Girls with Rett syndrome younger than 16 months of age have receptive language mental-age scores greater than expressive vocabulary scores, when compared with girls with Rett syndrome who are older than 16 months of age. Thus, regression in girls with Rett syndrome may be much more substantial than that occurring in children who develop ASDs before the age of two.

Fragile X Syndrome (FXS)

FXS is the most common¹² inherited form of mental retardation, resulting from a mutation in the *FMR1* gene on the long arm of the X chromosome (Xq27.3) that causes an unstable expansion of a CGG trinucleotide repeat in the 5' untranslated region of the gene. The length of the trinucleotide repeat determines the severity of the phenotype observed, ranging from **normal** (fewer than 50 repeats), to **premutation** (between 50 and 200 repeats), to affected or **full mutation** (more than 200 repeats). Although full mutation affects both males and females, premutation and full-mutation females may exhibit marked variability of phenotypic characteristics, depending on the extent of XCI. The FXS phenotype shows considerable variability, ranging from nearly normal functioning to severe cognitive impairment, with

¹² Lombroso, P.J. (2003). Genetics of childhood disorders: XLVIII. Learning and memory, Part 1: Fragile X syndrome update. *Journal of the American Academy of Child and Adolescent Psychiatry*, Mar;42(3), 372-5.

particular deficits in visual-spatial perception, speech and language, attention, self-regulation, and short-term memory.

In 2000, the NICHD, NIMH, and the Fragile X Research Foundation started a cooperative five-year funding commitment called the *Neurobiology and Genetics of FXS* (RFA-HD-00-015), which has led to substantial progress in biomedical, behavioral, and biobehavioral research in FXS over the past four years. The NICHD began funding FXS research well before the release of this RFA, with NICHD-supported efforts actually dating back to the late 1960s. For instance, NICHD funded cloning of the *FMRI* gene and its other counterparts, *Fragile X-related-1 (FXR1)* and *FXR2*, as well as studies on aspects of the neurobiology and cognitive effects of FXS for a number of years prior to the collaborative RFA. The Institute also supported work on the protein encoded by *FMRI*, Fragile Mental Retardation Protein (FMRP). FMRP localizes in the spiny protrusions of dendrites, where local protein synthesis may occur in response to stimulation by the neurotransmitter, glutamate. This research revealed that stimulation occurs through a specific subset of glutamate receptors, called metabotropic glutamate receptors (mGluRs). Mice that lack *Fmr1* have no response to stimulation by mGluRs and do not synthesize substantial local proteins in their dendrites. The dendritic spines in both humans and mice that lack FMRP are structurally abnormal, tend to be disoriented, and resemble those of young animals. Thus, FXS may represent a disorder in the “dendritic pruning” that occurs during normal development.

FRAGILE X MENTAL RETARDATION PROTEIN (FMRP) AND MRNAs

RNA binds to three locations on the *FMRI* gene—2 KH domains and one RGG box—as well as to FMRP. Once RNAs are bound, FMRP or its mRNA transports them along neuronal processes (particularly along dendrites) as large granules or clusters, called ribonucleoproteins. These clusters attach to microtubules and travel back and forth along the dendrites until they reach areas of synaptic contact, the dendritic spines, where they deposit their RNA “cargoes.” In the past two years, Institute-funded research has found that only a few hundred of these “cargoes” exist, and that most have a specific structure, known as a G-quartet, which binds only to the RGG box. Studies are now focused on proteins or mRNAs that bind to other structural motif domains; with these proteins identified, efforts could better define the “cargoes” being transported and the mechanisms of transport to provide possible targets for intervention.

Individuals, particularly males, with a full mutation make no FMRP because hypermethylation effectively “silences” the transcription of the gene. Further, FMRP acts as a translational repressor; phosphorylation mediates that process by effectively “stalling” FMRP on ribosomes, so dephosphorylation allows bound mRNAs to continue translation. Only very recently did researchers appreciate that this dephosphorylation step requires interaction with microRNAs, small non-coding RNAs that suppress translation by binding to target mRNA-complementary sequences.

Normally, *FMRI*-promoter methylation occurs after the global wave of methylation at implantation and involves specific targeting. The *FMRI* promoter resides within nucleosomes that contain specific methylated histones (primarily H3), which are associated exclusively with the process of forming heterochromatin (called heterochromatinization). *FMRI* binds to a particular protein, the Ezh2 polycomb protein, which in turn, recognizes the primary structure of the expanded trinucleotide repeat, and thus, plays a significant role in repression. Therefore, the

defect in FXS involves epigenetic silencing. When placed into embryonic stem cells, the defective X chromosome undergoes demethylation and reversion to an active *FMRI* gene. Upon differentiation, this X chromosome reinitiates inactivation, enabling testing of the role of *de novo* methylases, histone methylases and deacetylases, and polycomb genes and their complexes, such as Ezh2-Eed, in recognizing trinucleotide-repeat DNA structure.

FXS AND ASSOCIATED CONDITIONS

Previously, those with premutation genes (between 55 and 200 CGG repeats) were thought to be only minimally affected, if at all; but recent research provides interesting insights into the FXS premutation. For example, women with premutation alleles are at a 20-fold greater risk¹³ for premature ovarian failure—a term that describes a stop in normal ovarian function in a woman younger than 40 years of age—than full mutation females, or than women in the general population. Women with premutation also experience a high incidence of anxiety, depression, and learning difficulties and have weak math skills relative to reading skills and written language skills.

Males with premutation-sized alleles are at risk for a newly identified, progressive neurological disorder called fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS occurs in as many as one-third of premutation males—men usually in their 50s or 60s who have no prior physical or cognitive problems. These males are often grandfathers of full-mutation boys whose mothers are themselves premutation carriers.

FXTAS involves intention tremor, gait ataxia, and dementia and, less frequently, may include symptoms of Parkinsonism, peripheral neuropathy, and autonomic dysfunction (e.g., urinary/bowel incontinence and impotence). Neurological diagnoses among the original cohort of patients described with FXTAS varied, but included essential tremor, spinocerebellar atrophy, olivopontocerebellar atrophy, atypical Parkinson's, striatonigral degeneration, and multiple system atrophy. Females may also develop FXTAS, although the numbers are fewer and the onset of symptoms is earlier than in the males.

Because premutation expansions of the *FMRI* gene are frequent in the general population, with estimated prevalence¹⁴ of one in 260 females and one in 800 males, a lifetime risk of developing FXTAS within the general population may fall to at least one in 3,000 males. This incidence would make FXTAS one of the more common single-gene causes of tremor and ataxia, and of dementia in older adult populations.

The apparent absence of FXTAS among individuals with full-mutation alleles, combined with the finding that premutation carriers may exhibit substantially elevated levels of *FMRI* mRNA, may mean FXTAS results from a “toxic” gain-of-function of the *FMRI* mRNA. In fact, a higher CGG repeat number correlates positively with increased mRNA levels and significant brain atrophy and white-matter changes, including one pathognomonic neuroimaging feature—bilateral hyperintensity of the middle cerebellar peduncle. However, rare individuals with full

¹³ Hundscheid, R.D., Smits, A.P., Thomas, C.M., Kiemeny, L.A., & Braat, D.D. (2003). Female carriers of Fragile X premutations have no increased risk for additional diseases other than premature ovarian failure. *American Journal of the Medical Genetics Association*, Feb 15;117(1), 6-9.

¹⁴ Hagerman P.J., & Hagerman R.J. (2004). Fragile X-associated tremor/ataxia syndrome (FXTAS). *Mental Retardation and Developmental Disabilities Research Reviews*, 10(1), 25-30.

mutations exist whose *FMRI* gene is not silent and who may be at risk for FXTAS. Subgroups of such individuals include those with partially methylated full-mutation alleles (called methylation mosaics), repeat-size mosaics (both pre- and full-mutation alleles), and those with some gene activity despite extensive hypermethylation of the *FMRI* promoter region.

Young males with premutation alleles are similarly at risk¹⁵ for anxiety disorders and other conditions. For instance, ASDs may occur in as many as 70 percent of FXS boys who present clinically, in 17 percent of boys whose FXS a pedigree study detects, and in no normal male siblings who lack the premutation. Evaluation of full-mutation FXS males revealed no correlations among genetic parameters, CGG repeat number, FMRP, mRNA, and the presence or absence of autism. RiboCGG repeats introduced into mice and *Drosophila* produce RNA-mediated neurodegeneration, thus lending further credence to the “toxic” mRNA hypothesis. A recently created mouse model of FXTAS is now under scrutiny at several laboratories.

ADVANCES IN BIOCHEMICAL/METABOLIC RESEARCH

Biochemical pathways are fundamental to normal body and brain function. Changes in those pathways can disrupt not only the pathway itself, but also the processes and functions that rely on the pathway’s products and byproducts. The MRDD Branch funds research about biochemical processes and metabolism as these topics relate to brain functioning, brain injury, and long-term consequences to the brain. For instance, fetal hypoxia (low oxygen levels) may lead to severe hypoxic ischemic encephalopathy (HIE), a major problem worldwide; 10 percent to 60 percent of affected infants die, and at least 25 percent¹⁶ of survivors have long-term neurodevelopmental sequelae. Knowing the mechanisms of hypoxic injury may enable health care providers to prevent or even reverse the injury, which could improve outcomes for affected infants. The following section describes some recent findings of Branch-supported research on biochemical pathways.

HYPOXIA/ISCHEMIA

Molecular Mechanisms of Neuronal Cell Death Caused by Hypoxia

Nitric oxide (NO) from neuronal nitric oxide synthase (nNOS) mediates hypoxic neuronal injury and causes cell death by two distinct mechanisms. Glutamate receptors and an influx of calcium mediate one mechanism; specifically, selective nNOS inhibitors administered prior to hypoxia prevent the hypoxia-induced and glutamate receptor-mediated cascade of molecular changes that lead to neuronal cell death. Another mechanism involves activation of extracellular signal-regulated kinase and *c-Jun* N-terminal kinase that leads to neuronal death by increased phosphorylation of a programmed cell-death-repressor protein (Bcl-2). Thus, nNOS-derived NO

¹⁵ Reddy, K.S. (2005). Cytogenetic abnormalities and fragile-X syndrome in Autism Spectrum Disorder. *BMC Medical Genetics*, Jan 18;6(1), 3.

¹⁶ Vannucci, R.C., & Perlman, J.M. (1997). Interventions for perinatal hypoxic-ischemic encephalopathy. *Pediatrics*, Dec;100(6), 1004-1014.

results in hypoxic neuronal death by both transcription-dependent and transcription-independent mechanisms. Intervention with highly selective nNOS inhibitors, then, offers potential therapeutic strategies for preventing hypoxic neuronal injury in the newborn brain.

Neurons Defend Themselves from Hypoxic Damage

Extra- and intra-cellular signaling pathways confer vulnerability to and self-protection from hypoxic damage for neurons. Hypoxia induces sodium channel up-regulation. However, *in vitro* hypoxic preconditioning (HPC) protects neurons from subsequent severe hypoxia, and the δ -opioid receptor (DOR) is a critical participant in this protection. DOR protects neurons from sodium-channel over-expression during exposure to hypoxic stress. Neuronal responses to hypoxia depend on the depth and duration of the hypoxic condition; for example, intermittent hypoxia differentially regulates plasma-membrane sodium-ion channels in the developing brain by a duration-dependent process. DOR inactivation blocks this HPC-induced protection, meaning that intracellular up-regulation of survival signals regulated by DOR mediates HPC neuroprotection by this novel mechanism.

Protecting Glial Cells in the Developing Brain from Hypoxia/Ischemia

Characterizing the neuropathology of hypoxia/ischemia in human tissue and developing animal models of hypoxia/ischemia have facilitated the beginnings of translational research in the field. Periventricular leukomalacia (PVL) is a form of hypoxic/ischemic cerebral white-matter injury seen most commonly in preterm infants and is the major antecedent of cerebral palsy. Glutamate receptor-mediated excitotoxicity is a predominant mechanism of hypoxic/ischemic injury to developing cerebral white matter. In a rodent model of PVL, AMPA (alpha-amino-2,3-dihydro-5 methyl 3-oxo-4-isoxazolepropanoic acid) kainate-type glutamate-receptor blockade exhibits a protective effect. Examination of brain tissue from a hypoxic/ischemic-exposed human fetus revealed that developing oligodendrocytes in fetal white matter at 23 to 32 weeks' gestation, the period of greatest risk for PVL, expressed AMPA receptors. When administered post insult *in vivo*, topiramate, a clinically available anti-convulsant, protected against selective hypoxic/ischemic white-matter injury and decreased subsequent neuromotor deficits. In a rat model of hypoxia/ischemia, topiramate attenuated AMPA-kainate receptor-mediated cell death and calcium influx, as well as kainate-evoked currents in developing oligodendrocytes. Topiramate may protect by attenuating excitotoxic injury to pre-myelinating oligodendrocytes in developing white matter. The AMPA-kainate receptor antagonist NBQX (6-nitro-7-sulfamoylbenzo-(f)quinoxaline-2,3-dione) produces a similar result. AMPA-kainate receptor blockade, then, may have potential for translation as a therapeutic strategy for PVL. Notably, protective doses of NBQX and topiramate do not affect normal maturation or proliferation of oligodendrocytes, either *in vivo* or *in vitro*.

VERY LOW BIRTH WEIGHT/PRETERM INFANTS AND INTERVENTIONS

The Newborn Individualized Developmental Care and Assessment Program (NIDCAP) is a comprehensive program of interventions to protect preterm infants from the sensory onslaught of the newborn intensive care unit (NICU) environment. Although the NIDCAP is both very effective and widely accepted, the precise effects of the Program on the brain structure and function remained unknown, limiting understanding of how the interventions affected the

developing nervous system. An evaluation of the NIDCAP revealed that preterm infants (28 to 33 weeks' gestational age at birth) with no brain lesions were at risk for brain structure alterations resulting from traditional NICU environment and care, and that these alterations may lead to learning and other disabilities, even in medically low-risk preterm populations. This study provided strong and direct evidence that very early experience alters brain structure and function, a phenomenon known to occur in animals, but not previously documented in humans.

MATERNAL PHENYLKETONURIA (PKU) AND OTHER METABOLIC DISORDERS

Abnormal Concentrations of Fatty Acids in PKU

Adults and adolescents with PKU often maintain phenylalanine-restricted diets for most of their lives. Measurement of the plasma concentrations of fatty acids in such individuals revealed significantly elevated cholesterol/high-density lipoprotein ratios, ranging from 5.6-fold to 10.3-fold higher than normal. In addition, plasma docosahexaenoic acid (DHA) or arachidonic acid (AA) concentrations less than 50 percent of the level measured in controls accompanied these ratios. Because DHA and AA play important physiological roles in brain and retinal functions, the findings suggest that health care providers should monitor blood-lipid concentrations in all patients with PKU, including adults. Further, evidence suggests that clinicians should provide DHA and AA supplementation, particularly to those PKU patients with significantly reduced blood concentrations of these substances.

Pathogenesis of PKU in the Brain

White matter pathology observed in the forebrain of the PAH^{enu2} mouse, a genetic model for PKU, may result from perturbations in cholesterol synthesis. Studies of gross morphology and using electron microscopy demonstrated hypomyelination of select tracts in the forebrains of adult mice with PKU, but not in their hindbrains. Such hypomyelination correlated with a substantial decrease in the activity of the rate-controlling enzyme used in the cholesterol biosynthetic pathway of the forebrain, but not of the hindbrain. Oligodendrocytes, the cells that make myelin in the forebrain, were the source of the decreased activity, producing lower enzyme levels. In addition, *in vitro*, phenylalanine inhibited the enzyme in a non-competitive manner, so the enzyme is moderately inhibited in the PKU mouse. Unlike other cell types in the body, a subset of oligodendrocytes in the forebrain may be unable to overcome this inhibition, leading to the pathology observed in PKU brain.

Diagnosing and Treating Amino-Acid Metabolism Disorders

Some mutations in the genes that encode certain amino-acid synthesizing enzymes result in complex, sometimes fatal disorders that affect the brain and cause mental retardation. One such disorder, glutaric acidemias, arises from deficiencies in glutaryl-CoA dehydrogenase (GCDH), an enzyme involved in lysine and tryptophan synthesis. Investigators characterized the enzyme, cloned the gene, and identified numerous genetic mutations that cause human disorders; they then created mice with a targeted deletion of the *gcdh* gene in an attempt to model glutaric acidemias type I (GA-I).

Gcdh-null mice have a phenotype very similar to human GA-I patients and show increased concentrations of important metabolites (such as GA and 3-OHGA) that accompany spongiform myelinopathy in the brain. However, unlike human patients, the mutant mice showed no evidence of neuron loss or astrogliosis in the striatum, both important phenotypes in humans. This result illustrates that modeling complex human disorders is very difficult, even when the cause is “simple,” such as mutations in a metabolic enzyme.

While the search for a better mouse model continues, studies focus on improved prenatal diagnosis. Multiple-GCDH deficiency during pregnancy correlates with elevated alpha-fetoprotein concentrations in serum and amniotic fluid, as well as with cystic renal disease and fetal growth delay. These findings may help health care providers counsel couples whose children are at risk for metabolic disorders by identifying markers that are detectable during the first or early part of the second trimester. Defining a couple’s genotype also plays an important role in such counseling.

Studies of Mitochondrial Diseases

Branch-supported work indicated that clinical syndromes associated with point mutations in mitochondrial DNA (mtDNA) may be more diverse than those associated with point mutations in nuclear DNA.

MITOCHONDRIAL ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKE-LIKE EPISODES (MELAS) SYNDROME

Studies of the world’s largest cohort of MELAS patients—44 families with 131 fully symptomatic, oligosymptomatic, or asymptomatic subjects—have helped to define MELAS syndrome and to explore its treatment. By characterizing the clinical presentation and describing the natural history of MELAS syndrome, researchers better defined disease expression and progression, characterized associated medical symptoms, and established the frequency of life-threatening complications. Additional neuropsychological studies identified visual memory as the most vulnerable brain function in individuals with MELAS syndrome. Further, urinary sediment, not blood, provides the most reliable tissue to obtain data for diagnosis. One hypothesis currently under clinical trial investigation is whether chronic cerebral lactic acidosis exacerbates the clinical MELAS phenotype. Enrollment in a placebo-controlled, randomized, blinded clinical trial to test the efficacy of dichloroacetate for treating MELAS is also ongoing.

TREATING MITOCHONDRIAL DISEASE

“Allotopic expression” can correct mutations in enzymes of yeast. Recently, this strategy provided the first successful demonstration of mutation correction in the mitochondrial gene that encodes an energy-producing enzyme, ATPase 6 of complex V of the respiratory chain, in mammalian cells. This finding may provide the basis for a genetic approach to treating a number of human mitochondrial disorders.

MALNUTRITION

Malnutrition remains one of the most prevalent conditions affecting children. Mild-to-moderate malnutrition prior to two years of age delays cognitive development and leads to poor school performance later in life. Environmental factors, such as poverty and infection, may occur simultaneously with malnutrition and confound the results obtained by a majority of studies in human populations. Studies in animal models provide detailed information on the effects of malnutrition on the developing brain, and studies that use a multidisciplinary approach can contribute significantly to understanding the effects of prenatal malnutrition on cognitive development and brain function. The common rodent model recreates, as closely as possible, the conditions known to contribute to the occurrence of small-for-gestational-age babies in human populations.

Intergenerational studies of malnutrition involve rats whose mothers become malnourished by eating an isocaloric, protein-restricted diet containing identical amounts of vitamins and minerals. They are fed the diet for five weeks prior to pregnancy, and for the three weeks of pregnancy. At birth, cross-fostering to control dams nutritionally rehabilitates the experimental pups. Although small in size relative to well-nourished control pups, the experimental pups are otherwise healthy.

Tests of the experimental rats over their lifespan (from embryonic stages to adulthood) revealed adverse effects on cognitive performance, emotional reactivity (including stress responsiveness), and social interactions. In particular, prenatal protein malnutrition affects the inhibitory neurotransmitter, GABA, and produces negative physiological effects in *in vivo* long-term potentiation, kindling, paired-pulse measures, and *in vitro* miniature inhibitory postsynaptic currents.

Prenatally malnourished rats also respond abnormally to a variety of psychological and physiological stressors. Examination of the effects of stress on measures of neurobiological development and function in the neonatal malnourished rat showed that stress excessively activated immediate early genes that regulate brain function. In prenatally malnourished rats, stress in the neonatal period also altered both neurogenesis and the apoptotic pruning of excess neurons in the hippocampal cortex. Despite the relative preservation of prenatal neuron development in the brainstem (e.g., locus coeruleus and raphe nuclei), prenatal malnutrition disrupted postnatal processes that underlie normal plasticity.

ADVANCES IN BEHAVIORAL AND BIOBEHAVIORAL RESEARCH

In addition to biological and biochemical studies of various developmental disabilities, the Branch also supports research on the behavioral and biobehavioral characteristics of MRDD. In some cases, knowledge about the biological or biochemical mechanisms of these disorders may help explain the behavioral characteristics common to persons affected. In other cases, knowledge of the behavioral symptoms may shed light on the biological or biochemical mechanisms that cause these disorders. The following section describes some Branch-supported work in behavioral and biobehavioral research.

AUTISM SPECTRUM DISORDERS (ASDs)

Autism is a severe developmental disability that is evident in infancy or during the early preschool period and affects some of the most essential human behaviors, including the ability to communicate feelings and ideas, interact socially, and establish and maintain relationships with others. The ASDs include classic autism or autistic disorder, Asperger syndrome, Rett syndrome, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder – Not Otherwise Specified. Through the MRDD Branch, the NICHD supports the CPEA Network and the STAART Centers to learn more about autism and ASDs (see [Figure 2](#) and [Appendix B](#)).

Among supported projects is one in which researchers fully evaluated and collected DNA from 300 multiplex families—the largest existing sample of multiplex families on whom investigators have collected extensive phenotype measures for all family members. The investigators are currently conducting genetic linkage analyses with these data. In addition, the CPEA Network recently adopted the quantitative measures of the autism phenotype that investigators developed for the linkage study as the common phenotype measures for studies Network-wide. The following section highlights some recent findings from Branch-supported autism research.

Etiology and Pathophysiology—Brain Studies of ASDs

Using electrical brain responses measured from the scalp ERPs, grantees detected abnormalities in brain function in very young children with autism or ASDs. Researchers showed that, by six to seven months of age, normally developing babies display differential brain responses when they view familiar faces versus unfamiliar faces, and when they hear different speech sounds. Three-year-olds with autism failed to show different brain responses when they viewed photos of their mothers and photos of unknown persons, and when they heard different speech sounds. These important findings could lead to: possible new ways of identifying autism in very young infants; insight into specific brain regions affected in autism; and a possible genetically mediated functional marker of vulnerability to autism.

Another MRDD Branch grantee used MRI to demonstrate that three- and four-year-old children with autism have enlarged brains when compared to developmentally delayed and typically developing children the same age, suggesting that autism involves an abnormal process of brain growth that takes place very early in its clinical course. This study represents the first comprehensive examination to use MRI on one of the youngest sample of children with autism and well-matched comparison groups. This sample is also the youngest for which investigators

documented abnormal brain size systematically. To build on these findings, current NICHD-funded studies examine longitudinal course of brain development in this group of children at ages three, six, and nine, as well as brain structure and growth in infants and toddlers with autism.

Two theories aim to account for these larger-than-normal brains of individuals with autism: one theory suggests that the size results from a failure of normal cell death (apoptosis) during the perinatal period; the other suggests the size results from progressive failure of synaptic pruning during the postnatal period. Magnetic resonance spectroscopy studies can distinguish between these alternative hypotheses by measuring the children's levels of N-AcetylAspartate, choline, and creatine—chemicals that provide an index of neuronal density and brain tissue viability, and that exhibit distinct “chemical” signatures. Levels of these brain chemicals distinguished the children with autism from normal children and from those with developmental delay. Children with autism showed significantly lower levels of all three chemicals; this finding does not support the faulty apoptosis hypothesis.

This same group of investigators also found that one brain structure—the amygdala—was proportionally larger relative to an overall enlarged brain in children with autism. The size of the amygdala correlated with the severity of autism symptoms and predicted the child's clinical course over the preschool period. MRDD Branch-funded investigators are now examining whether early measures of brain structure and chemistry predict how a child responds to early behavioral interventions.

Diagnosis and Evaluation—New Screening Tools

The genes that contribute to the development of autism remain elusive, which likely reflects differences in the specific genes that cause the disorder in individuals and in families. MRDD Branch grantees are characterizing a group of individuals who share a common genetic basis for the condition—a short duplication on the long arm of HSA15—the most common chromosome abnormality found in individuals with autism. The research team developed a new microarray tool that allows rapid screening for evidence of duplication, defines the amount of HSA15 that is duplicated, and determines the number of copies present. This new tool allows examination of duplications in those with known HSA15 abnormalities and provides an excellent rapid screen for hidden duplications in those who are not known to carry a chromosome abnormality.

Because autism is difficult to detect in the very young, referral for evaluation occurs later than would be optimal for many children. Early screening of young children is essential to help minimize the delay in diagnosis and resulting intervention. What had been lacking was a brief parent-reported screening tool to alert health care providers of the need for further evaluation in children who show early signs of possible autism. An NICHD grantee created the Modified Checklist for Autism in Toddlers (M-CHAT) to meet this need. After administering the M-CHAT to 1,200 children and evaluating those who screened positive for autism, concurrent and predictive sensitivity ranged from 85 percent to 95 percent, which suggests that health care providers should evaluate those who screen positive on the M-CHAT further for autism.

Investigators translated the M-CHAT into many languages (i.e., Spanish, Chinese, Turkish, and Japanese), and it is currently in use in trials in several countries and in multiple sites throughout the United States. In addition, the American Academy of Pediatrics endorsed the tool, meaning

that the M-CHAT may become a standard screening instrument in pediatrician's offices. Its use will greatly improve early identification of autism and will allow toddlers to receive early intervention services.

Diagnosis and Evaluation—Sensory Symptoms and Autism

Individuals with autism show unusual responses to sensory stimuli; in fact, such responses are part of the symptomatology of autism. Several theories of autism suggest that the sensory symptoms may be primary to the disorder and may lead to the social and other symptoms characteristic of the condition. MRDD Branch-funded studies demonstrated that, very early in life, sensory symptoms did not relate to social/communicative behavior in autism and did not distinguish children with autism from children with other disorders, such as FXS. Instead, the presence of repetitive behavior was the characteristic that distinguished children with autism from those with other disorders. Further, these distinctive behaviors related only to diagnosis, not to IQ. These findings suggest that repetitive behavior is a more autism-specific feature, but that it is not necessarily related to sensory responsivity.

Amelioration and Other Studies—Randomized, Controlled Joint Attention and Symbolic Play Interventions

Because the symptoms of autism are so varied, interventions that are effective for some people with autism may not be useful to others. MRDD Branch-supported researchers examined the efficacy of targeted interventions aimed at joint attention (i.e., the ability to follow an adult's gaze or to point/gesture at an object) and symbolic play (i.e., pretending). Their analyses yielded significant differences: children in the targeted interventions groups outperformed those in the control group. Also, children in the targeted joint attention intervention group improved in their joint attention skills, while those in the symbolic play intervention group improved in their symbolic play skills. Skills generalized from the experimenter to the parent and maintained over the one-year follow up.

Interestingly, children in both intervention groups made significantly greater gains in language development over the one-year follow-up period than the control group did. Language development by age five or six remains one of the most powerful predictors of good social outcomes for children with autism, meaning that these interventions hold promise for broader improvements.

Amelioration and Other Studies—Autism in Toddlers with Fragile X Syndrome (FXS)

Patients with FXS are consistently described as “autistic-like,” but no study had compared the symptoms of FXS to those of children with autism. Results of an MRDD Branch-funded effort found that one-third of very young children with FXS had the full syndrome of autism as measured by state-of-the-art tools¹⁷. In addition, the characteristics of these children made them distinctly separate from non-autistic children with FXS. These findings suggest that children with both FXS and autism have additional background alleles that may interact synergistically with the *FMR1* mutation to cause autism. The *FMR1* mutation may dramatically predispose a child to autism and may help researchers identify autism-specific alleles more rapidly.

¹⁷ Rogers, S.J., Wehner, D.E., & Hagerman, R. (2001). The behavioral phenotype of Fragile X: Symptoms of autism in very young children with Fragile X syndrome, idiopathic autism, and other developmental disorders. *Developmental and Behavioral Pediatrics*, Dec;22(6), 409-417.

SELF-INJURIOUS BEHAVIOR (SIB)

SIB associates with a number of conditions that involve intellectual and developmental disabilities. In young children with disabilities, SIB may emerge before age three and is mostly not related to social situations (called non-social); older children who self-injure are often sensitive to social consequences, such as not gaining a preferred item or caregiver's attention, or trying to escape non-preferred situations. A number of interventions have had varying success in treating SIB when automatic reinforcement maintains the problem behavior (i.e., the behavior continues when the individual is alone). Blocking procedures that force an individual to choose among alternatives may also prove useful. Even though some topographies of SIB (i.e., where on the body the self-injury occurs) appear to be interchangeable, others are not.

Parents of young children who exhibit SIB can deliver treatments themselves, learning effective functional communication training for the very young. Non-social SIB associates with problems in sensing and regulating pain. Studies of salivary biomarkers, such as substance P and cortisol, help to understand these phenomena. For instance, among those who chronically display SIB, abnormalities occur in the pain fibers that innervate the skin; not only do the nerve bundles course abnormally in the skin, but their distribution and spacing is also irregular and infrequent. Cortisol homeostasis is also dysregulated, with blunting of the diurnal rhythm and elevated evening levels.

The symptoms of SIB worsen in many individuals who reside in institutional settings as they age; increased abnormal movements and, ultimately, increased behavioral disturbance may also occur. Stereotypies arise from a neural circuit that links the cortex to the striatum and eventually back to the cortex; drugs that target this circuit, particularly the striatum, are useful for treating SIB. For example, adults with repetitive movements and Pervasive Developmental Disorder display significant reduction in stereotypy, social withdrawal, and irritability, have reduced prolactin levels, and display decreased dyskinesia without other side effects when treated with olanzapine. Although no category of abnormal repetitive behavior is unique to autism, SIB strongly associates with social events, and stereotypy is less sensitive to environmental changes.

LANGUAGE AND COMMUNICATION DEVELOPMENT, LEARNING COGNITION, AND MEMORY

Language Studies

Children with Down syndrome experience exceptional difficulties with language development, particularly in the area of syntax. Because visual memory is a relative strength for these individuals, in comparison to auditory memory, intervention strategies that focus on predominantly auditory syntax may prove less effective in this group than for children with stronger auditory skills, such as those with WMS. Etiology-specific intervention would prove clinically useful in these cases.

Although relatively rare, WMS has been at the center of critical debates about the nature and causes of language development in typical, as well as atypical populations. Typically developing children tend to have equivalent levels of skill in language and in non-verbal cognition; children

with WMS are more advanced in language, while children with Down syndrome show the opposite pattern, although both are delayed relative to typically developing children. Studies of these three groups have helped determine what factors are universal and necessary to lexical, communicative, and grammatical development, and what factors are specific to particular rates or paths of language acquisition.

Wide individual differences in language growth among individuals with WMS tie to cognitive development, and those with WMS have substantial and unique needs in regard to educational and therapeutic interventions that target language. Clinically, the trajectory of early lexical development—the shape of the lexical growth curve—rather than the static profile or the diagnosis predicts later communicative and grammatical development provides a novel way to address questions of cross-syndrome differences in language development.

Individuals with WMS also exhibit a preservation of language function, as well as an increased receptivity to sound and musicality. Individuals with WMS make significantly greater use of affective language, regardless of their culture of origin. Facility using language is an undisputed strength in individuals with WMS, even though reduced prosodic and paralinguistic competence occurs in other mental retardation syndromes.

Communication Development and Speech Intelligibility

An MRDD Branch-supported longitudinal study compared communication development of preschool- and elementary-aged males with FXS to males with Down syndrome and typically developing males who were younger. Boys with FXS showed better non-verbal mental skills than expressive vocabulary or speech, and better receptive than expressive vocabulary. Boys with Down syndrome also had better non-verbal mental skills than expressive vocabulary or speech, but had better expressive vocabulary than speech. Typically developing boys showed no differences in skills.

Males with FXS used shorter, less complex sentences and words than did typically developing males and showed delay in syntactic skills compared with non-verbal cognitive skills. Although males with FXS and those with Down syndrome exhibited approximately the same rates of growth in expressive and receptive vocabulary, cognitive skills and autism status served as important predictors of language growth. Genetic status of FXS did not independently predict receptive or expressive vocabulary.

In addition, although FXS males exhibited delay in speech development, they showed typical speech patterns, and they made fewer pattern errors than did Down syndrome males, who exhibited delay in speech development, especially in phonological development. Males with FXS had poorer oral structure, speech, and non-speech motor function than did typically developing males, but had better oral motor and speech motor function than did Down syndrome males. Down syndrome males did better than FXS males on non-speech function tasks, but did worse on all other outcomes.

Several studies showed that every intellectual disability has associated strengths and weaknesses with respect to speech and language that need to be identified to tailor the learning experiences and to achieve the most meaningful results. Thus, one type of teaching strategy will not necessarily be effective for all children with disabilities; rather, each child will benefit from an

individual educational strategy designed specifically for him or her that builds on individual strengths and helps to identify and ameliorate individual weaknesses.

In another MRDD Branch-supported study, researchers examined speech intelligibility, which, when poor, can compromise all aspects of communicative interactions, regardless of developmental status. FXS males showed greater delay in phonological development than did younger typically developing males, but their phonological characteristics in isolated words were similar to younger typically developing males. Down syndrome males showed both greater delays and developmental differences compared to FXS and typically developing males and performed better than those with FXS on non-speech function tasks and did worse than FXS males and typically developing males on all other outcomes. FXS and Down syndrome males showed less typical oral structure and motor function than younger typically developing males; they also differed in their mastery of coordinated speech movements. FXS males spoke faster than developmentally age-matched males, and, although the vowel spacing was similar, FXS males made significantly shorter utterances and tended to pause less often than chronologically age-matched males. Thus, differences in utterance length and pausing account for common perceptual characteristics attributed to speech, such as rapid, garbled, and perseverative speech, in males with FXS.

The Brains of Individuals with Autism and Language Development

Typically, the two halves of the human brain are asymmetric in size; the left hemisphere is larger than the right and this difference relates to human language capacity. This asymmetry appears before birth and remains constant throughout life. Typical brain asymmetry is absent in adults with autism compared to well-matched controls, and the autism group has reduced volume of the left planum temporale, a structure related to the auditory processing of language. The degree of asymmetry present directly relates to the language ability of the subjects. Interestingly, children with autism exhibit a parallel hemispheric symmetry. These findings link a specific brain abnormality found in autism with language impairments, a primary symptom of the disorder.

Defining specific brain abnormalities of autism is critical to developing cognitive rehabilitation or definitive biological treatments for autism; brain circuitry or connections likely underlie these abnormalities. A group of MRDD Branch-funded studies used functional MRI (fMRI) to show that individuals with autism (but who were not mentally retarded) had word skills superior to normal controls, but had inferior sentence-understanding skills, even when both groups spoke the same sentence. The brains of persons with autism showed over-activity in the word-analysis area and increased connections in local brain circuitry (over-connectivity), but under-activity of sentence areas and reduced connections among the multiple regions of the brain (under-connectivity) needed for sentence understanding. This major advance in understanding the brain basis of autism will help in designing new cognitive intervention strategies that stimulate development of the under-connected circuitry, while they discontinue activities or class work that may contribute to increased connectivity within the circuitry.

Studies of Cognitive Function

The most common feature of Down syndrome is intellectual disability in the form of mental retardation. Investigators believe that over-expression of several genes located on HSA21 may contribute to the behavioral and cognitive phenotype of Down syndrome. Although epigenetic factors or environmental influences may account for as much as 70 percent of the factors that

affect nervous system development, neurons have to receive, process, and transmit information properly to promote effective and efficient cross-talk within the nervous system. Cognitive studies of individuals with Down syndrome now begin with populations of infants and continue through studies of the “oldest old” with Down Syndrome, individuals older than 60 years of age. For example, ERPs enable investigators to “watch” the dynamic aspects of brain function in infants from a few weeks of age, through the toddler period, and into the preschool period. This type of research allows prospective longitudinal study of how brain function within cognition develops, how rapidly this function changes, what the sequences of the changes are, and how different profiles associate with specific developmental disabilities and at-risk populations.

Cognitive brain function develops so rapidly within the first year of life that distinct and meaningful neural changes can occur during half-week intervals. For example, typically developing four-month-old infants demonstrated that they can learn more quickly than investigators anticipated, and that they do have long-term memory. Some, but not many, infants with Down syndrome do not express significant developmental delays but express robust developmental milestones. Thus, variation in ERPs can enable prediction of cognitive development during first year of life and may help to assess the outcome of early interventions.

Research from birth also helps refine early interventions and identify those infants most in need of intensive early intervention. ERP profiles are distinctive and can identify infants who do not have known genetic conditions, but who express non-normative neural development and, thus, may be at developmental risk. These children may later receive a diagnosis of ASDs, FXS, attention deficit/hyperactivity disorder, dyslexia, dyspraxia, and specific language impairments.

Just as different MRDD conditions show unique speech and language strengths and weaknesses, so too do they have unique cognitive strengths and weaknesses. For instance, children with PWS are not only interested in puzzles, but also excel at them relative to mental age-matched controls. Individuals with PWS have a better perception of curves (shape) and tend to match colors, but do not correct for spatial location within a puzzle. When older individuals with PWS self-select leisure activities, they choose fewer musical activities, while those with WMS chose fewer visual-spatial activities (i.e., arts and crafts and puzzles) and physical activities (i.e., swimming and bike riding). Males with WMS choose more physical activities than do females with WMS, while males with Down syndrome choose more electronic activities (i.e., playing computer games). Overall, individuals with WMS choose more musical activities than do either individuals with PWS or Down syndrome. Individuals with Down syndrome choose more visual-spatial activities than do individuals with WMS, and individuals with PWS choose more competitive visual-spatial activities, such as playing board and card games, than do individuals with WMS.

Individuals with autism also have unique cognitive characteristics. In one MRDD Branch-funded fMRI study, verbal adolescents and adults with autism (who were not mentally retarded) and controls viewed letters in various contexts. In the brains of normal individuals, this task activated the left-frontal language region of the brain, while, in the brains of individuals with autism, the task activated the right-posterior visual part of the brain. Thus, although the groups did not differ distinguishably in performance, the individuals with autism differed fundamentally in how understanding occurred, using a non-language approach. The results of fMRI analyses were similar for other tasks, but the outcomes were not as dramatic.

This finding provides the basis of the common breakdown in communication that occurs between individuals with autism and other people. Health care providers and educators cannot assume, then, that individuals with autism use the same cognitive processes as individuals who do not have autism, even when the behavioral performance is the same. Further, one cannot base intervention methods for individuals with autism on models of normal cognitive processing; instead, methods need to incorporate further understanding of the unique way individuals with autism see the world and process information.

Brain Differences in the Processing of Faces

MRDD Branch-supported researchers found that although individuals with WMS exhibit strengths in processing faces, they have spatial-processing deficits and have difficulty transforming environmental spatial information into a coherent representation. Individuals with WMS use a global processing strategy to process faces qualitatively. This strategy allows them to detect human faces earlier in life than do typically developing individuals because they view faces as low-frequency pixilated information, like an image.

The associated brain-processing deficits that underlie deficits in social behavior, among the central defining features of autism, also remain poorly understood. Major advances in understanding facial processing in the brain come from two recent CPEA Network studies. First, facial processing in the brains of higher functioning children with autism differed from children with Asperger disorder. Specifically, the brains of children with autism did not use the fusiform gyrus—the area that normally performs facial processing—to process faces. Instead, the brain processed faces using the area that usually processes objects. A second, but related line of study used eye-tracking movements to document face-scanning patterns. Findings from this study appear in the *Social and Affective Development* portion of this section.

FAMILY FUNCTIONING AND FAMILY AND COMMUNITY INTERACTIONS

A major objective of effective newborn screening is to allow family support and intervention to begin as early as possible. Challenges and disruption associate with a family's adaptation to a child's diagnosis over time, even though parental responses may vary. Multiple levels of contextual influence are important, and the potential for positive family perceptions and resilience exists and requires reinforcement.

For instance, mothers whose children have FXS (and who have passed the gene onto their children) are more likely than mothers of children with other developmental disabilities to have problems with maternal guilt. This finding¹⁸ holds true even though mothers of children with Down syndrome are likely to be the source of their child's extra chromosome. Mothers of children with FXS actively and consistently seek support and information. Because correct diagnosis of FXS may take several years, uncertainty is also a major theme for these women. In addition, more parental support groups exist for families affected by Down syndrome than for

¹⁸ Abbeduto, L., Seltzer, M.M., Shattuck, P., Krauss, M.W., Orsmond, G., & Murphy, M.M. (2004). Psychological well-being and coping in mothers of youths with autism, Down syndrome, or Fragile X syndrome. *American Journal of Mental Retardation*, May;109(3), 237-254.

families affected by FXS, and the literature often overlooks the positive characteristics of children with FXS, adding to the burden of mothers of children with FXS. Timely and sensitive family support is important for any family with a child who has MRDD, but these findings indicate that it is especially important for families affected by FXS.

Family processes also play an important role in self-regulation of children with Down syndrome. Both family process and children's self-regulatory deficits influence the dual diagnosis of Down syndrome and difficult behavior that may arise during adolescence. Although parents may use distraction and language to regulate these behaviors for younger children at home, family interactions influence the children's social skills and interactions and affect peer relationships and other social outcomes when the children are at school or in the community. Family assistance in coping with social rejection influences a child's ability to process social information, and to solve social problems. Many families direct their efforts at arranging and monitoring social encounters to increase their children's social participation and improve social skills. These families need services and assistance to facilitate this social competence and to promote positive social outcomes for their children.

Research shows that families of children with MRDD are clearly resilient in meeting the special demands they face. Efforts to involve these children in discussions of problems do not disrupt parents' interactions with other children, nor does this inclusion cause greater negativity. In addition, although fathers are typically more likely than mothers to have negative interactions with difficult children, the same is not necessarily true of difficult children with MRDD. Fathers also appear more sensitive to important dynamics of family systems that impact members with MRDD, than do mothers or other family members. Relationships with siblings also improve positive social adjustment with peers, and maternal warmth improves a child's adaptive functioning over time.

Adjustment in families rearing children with MRDD is complex and involves parents, typically developing siblings, and children with MRDD. These individuals interact in ever-changing ways both with each other and with the outside world, over a life-course that is far from static. In the 1980s, the prevailing view of these families was one of pathology and maladjustment. Over the past decade, however, studies that compare families who knowingly adopted children with disabilities with families who had similar children by birth have challenged this view. MRDD Branch-supported researchers expected adoptive parents to adjust better, especially early on, after the initial crises; but they found that birth families also adjust quite well to the challenges posed by rearing a child with disabilities. Few differences were obvious when the children were an average of six years of age. When the children were 11, however, some differences emerged. Depression rose slightly, but significantly, for both adoptive and birth mothers, but more so for birth mothers. The most noticeable difference observed between adoptive and birth mothers occurred in a personality measure of mental stability/instability.

Another stressful time for these families is their children's transition to adulthood. At this stage more than other stages, parents confront a complex and unorganized group of programs that do not ensure availability, accountability, or appropriateness. Such challenges increase differences in adjustment between the relatively more- and less-stable parents. Stable and enduring factors, such as personality traits and religious beliefs, help to predict how well parents cope with their children's transition to adulthood.

Further, observations of how adoptive and birth families interact in at-home situations helps better assess how family members affect one another. Follow-up studies will provide additional data to better guide the design of support services.

Foreign Communities and MRDD

Recently, the MRDD Branch participated in outreach to Asian populations through international funding initiatives in collaboration with the Fogarty International Center at the NIH. This outreach seeks to stimulate studies of the incidence and epidemiology of conditions, such as Down syndrome, FXS, and WMS in, for example, China. The initiative also supports studies of cultural variations in attitudes and interventions that result from widespread newborn screening programs. The MRDD Branch supports planning grants to establish infrastructure that will facilitate individual cooperative research programs in these areas.

SOCIAL AND AFFECTIVE DEVELOPMENT

Although the MRDD Branch supports research on social and affective development in many MRDD conditions, recent findings relating these topics to autism are particularly noteworthy. For this reason, the Branch report now highlights some autism-related findings.

Quantifying Social-Visual Pursuit in Individuals with Autism

A novel set of CPEA Network studies has developed technology to use eye-tracking methods to quantify social-visual pursuit in naturalistic situations. Individuals with autism exhibit atypical patterns of eye movements as they view social situations. Individuals with autism prefer to focus on less essential or even irrelevant aspects of social stimuli (e.g., mouths, objects) rather than on the eyes. Investigators used data analysis methods that quantify the dispersion of visual fixation moment-by-moment to create “funnels of attention” (e.g., as these dispersions expand and contract) that map onto social scenes as the situations unfold in front of a group of viewers. Because visual attention to salient aspects of the social environment is a highly conserved skill that emerges in the first weeks of life, health care providers may use these methods to identify vulnerabilities to autism prior to the manifestation of symptoms. Identifying these features in the first year of life (if not in the first six months of life) opens the possibility for early interventions that capitalize on neuroplasticity and, hopefully, maximize positive prognoses for these children.

A related study focuses on the prospective follow-up of siblings of children with autism; these siblings may themselves develop autism. This follow-up relies on eye-tracking methods, begins at birth, and continues monthly for the first two to three years of life. The ontogeny of social-visual engagement traced by eye-tracking methods allows quantification of the attentional resources that infants devote to different aspects of visual stimuli, such as physical properties (e.g., luminosity, movement, high/low spatial resolution, etc.), as well as object perception (e.g., inanimate and social objects). Careful focus on the maturational and perceptual/cognitive aspects of the social-visual system, which is functional from the first few weeks of life, may identify the time when the earliest divergence from normative patterns occurs in infants with autism.

The Social Brain, Joint Attention, and Autism

During the first 18 months of life, social impairments in children with autism are most clear in terms of disturbances in social orienting and related problems with joint attention skills, which involve the capacity to follow gaze direction and the pointing gestures of others (called Responding to Joint Attention or RJA), or the capacity to share the experience of an object spontaneously with others using eye contact, showing, or pointing (called Initiating Joint Attention or IJA). Children with autism have great difficulty mastering these skills, and measuring deficits in these skills could greatly improve the early identification and diagnosis. An MRDD Branch-supported study found that electroencephalographic activity in the frontal lobes of the brain at 14 months predicts IJA development at 18 months in typically developing infants; alternatively, activity in the parietal lobes predicts RJA development over the same time frame in the same group. Problems in frontal lobes associate with attention control and self-monitoring, and problems in the parietal lobes associate with processing information about other people; such problems may underlie joint attention impairments in autism. An independent study using a tool for measuring joint attention development called the Early Social Communication Scales found that activity in the brain regions involved in IJA at 14 months of age predicts language development at 18 months of age, a relevant finding because children with autism often exhibit language delays.

In addition, an evaluation and analysis of available peer-reviewed neuroscience literature on social development, social cognition, and autism led to a new theory; joint attention reflects the integration of at least two systems. First, the parietal and temporal brain regions serve a *social attention system* that processes information about other people. Second, dorsal and medial frontal areas of the brain (e.g., the anterior cingulate) serve a *self-attention system* that processes and monitors information about one's own social behavior. Social disturbances in autism may reflect deficits in one or the other system or, more likely, in the integration of (or communication between) these systems. This theory has led researchers to refocus attention on the role of the anterior cingulate in autism; it suggests that the role of the frontal cortex and anterior cingulate in attention regulation and in dividing attention across multiple channels (e.g., integrating attention to self and other) may be *fundamental* to the nature of autism.

Following the framework of this theory, IJA development in infancy relates to a self-recognition measure of self-monitoring. A detailed and integrated neuro-functional model of early RJA and IJA development describes how impairment in joint attention development may, itself, contribute to subsequent neural impairment and disorganization in autism. Further, preliminary electrophysiological data are consistent with results from imaging studies and support the hypothesis that some types of differences in anterior cingulate activity relate to social and intellectual deficits in children with autism.

Problem-Solving Skills and Emotional Responses in Autism

An extensive battery of abstract-reasoning and problem-solving tests taken by adolescents and adults with autism and normal controls revealed surprising results in terms of the repetitive and restricted behaviors common in autism. Although members of the group with autism could identify concepts and apply rules, they incompletely understood the concepts; as a result, when the context changed, they could not change the application of the rules. They also had little capacity to develop or create new strategies for solving problems on their own. Further, associated conceptual skills, such as insight and judgment, were also lacking in individuals with

autism. Thus, restricted and repetitive behavior in autism has a cognitive basis—that is, a focus on details and rules—but also stems from a lack of understanding of concepts. As a result, persons with autism have serious problems with adaptive functioning in real life because they cannot apply what they are taught to ever-changing situations.

A recent series of fMRI studies focused on social communication and on understanding the neural basis of fundamental deficits seen in autism, namely, emotion processing, imitation, empathy, joint attention, and non-verbal communication. For instance, facial expression and tone of voice convey important information about the speaker's intent, but perceiving and appropriately processing this information are impaired in individuals with autism at all levels of severity. Children with autism show reduced brain activity in emotion-relevant networks, but only when affective cues require automatic processing. In contrast, when a task allows more cognitive or explicit processing of emotional information, the pattern of brain activity for children with autism is remarkably similar to patterns observed in typically developing children. Thus, treatments aimed at providing explicit instructions for processing emotional information may successfully engage brain regions essential for these functions in children with autism.

EARLY IDENTIFICATION AND INTERVENTION FOR AT-RISK POPULATIONS

Effectiveness of Treatments for Women At-Risk for PKU

The NICHD recently completed the Maternal PKU Collaborative Study, the largest and most definitive clinical study of maternal PKU to date. The 18-year study was prospective, longitudinal, and observational and included more than 120 clinics in the United States, Canada, Germany, Switzerland, and Austria that used a uniform research protocol. When the study ended in 2002, researchers had accumulated an enormous wealth of information about maternal PKU, and a knowledge base that extended well beyond the initial objectives of the study. The primary results appeared in a supplement to *Pediatrics* in 2003¹⁹.

The findings clearly demonstrated that restricting phenylalanine in the diets of women with clinically significant hyperphenylalanemia during pregnancy decreases the incidence of intellectual disability, microcephaly, congenital heart disease, and intrauterine growth retardation in their offspring. Treatment was most effective if begun before conception and/or during the first six weeks of pregnancy. The greatest barriers to timely treatment were psychosocial problems and public health obstacles. In addition, the findings indicated that if health care providers do not identify women with PKU consistently and treat them appropriately, at-risk women could bear more children with MRDD (and congenital heart defects, which is not a characteristic of PKU itself) than were born with PKU prior to effective newborn screening. This observation emphasizes the importance of monitoring long-term outcomes of children detected and treated through newborn screening programs.

The long-term study greatly heightened public and medical-community awareness of maternal PKU and demonstrated the effectiveness of treating it for both mother and child. As a result, women with PKU and their health care providers now understand the importance of timely and continued dietary intervention for ensuring healthy children.

¹⁹ *Pediatrics*, Dec;2003; 112(6), 1513-1587.

Studies in Young Children With, or At Risk for, Autism

One CPEA Network study of children with autism focused on early development in ASD, particularly on the phenomenon of early loss of skills or regression before age three and sought to standardize the measures and definitions of loss associated with regression. Overall, caregivers described children who had used words spontaneously and meaningfully, but who then stopped talking, as showing more gestures, greater participation in social games, and better receptive language before the loss, and showing fewer of these skills after the loss. These findings reaffirm that these children experienced a “regression,” and that they are different from other children with ASDs. Furthermore, a significant minority of children with ASD but without word loss showed a very similar pattern of loss in social-communication skills that was not observed in children with developmental delays or with typical development. Thus, early regression is a specific, though not universal feature, of ASD. These results may help improve methods of early detection, as well as the potential for early intervention and better long-term outcomes.

Another study of the same sample of children focused on the relationship between a regressive phenotype of ASD and the measles-mumps-rubella (MMR) vaccine. Caregivers described children who had acquired skills and subsequently lost skills as showing a greater number of skills prior to the age of 24 months, and showing fewer of these skills than other children with ASD by 36 months of age. Children who experienced losses also showed poorer outcome in verbal IQ and social reciprocity, a later mean age of onset of autistic symptoms, and a greater number of gastrointestinal symptoms than children with ASD who did not regress. Overall, there was no evidence to suggest that onset of autistic symptoms or of regression relate to the MMR vaccination.

ASSISTIVE TECHNOLOGIES

Individuals with MRDD live longer today than ever before. As they integrate into the mainstream of daily life, they face unique problems in the routine aspects of everyday living that often interfere with their quality of life. Life events that seem simple to typically developing children and adolescents, such as calculating correct change for or after a purchase, getting directions, reading maps, conversing with strangers, and keeping a daily schedule, are often difficult for those with MRDD.

The MRDD Branch funds research to develop assistive devices that improve an individual’s mental and physical health. The MRDD Branch also funds development of devices for measuring and diagnosing the biobehavioral phenotypes of individuals with disabilities. Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) mechanisms provide most of the funding for these endeavors. This important research enables rapid translation of basic behavioral and biobehavioral research findings from the MRDD field into means to improve the lives of individuals and their families, and to minimize the burden on the society.

Some assistive technology advances of interest include the following:

- Although techniques to improve sequencing skills, which are required for the development of reading, spelling, and numeric skills, in individuals with MRDD exist, these individuals, health care providers, or parents who might benefit from them cannot readily access most of them. One MRDD Branch grantee created user-friendly software for computer-assisted instruction based on a form of “constructed matching to sample.” This software benefits parents and health care providers, such as special educators, psychologists, and speech/language pathologists. Another program, based on sequence-teaching methods, is the Picture Reader, which teaches students to “read” pictures instead of words. The pictures serve as instructional stimuli for acquiring sequencing skills needed for task completion.
- A video and workbook materials teach parents with cognitive limitations how to rear their children, ages two year to five years old. First, the parents learn how to establish routines. Subsequent lessons explain how to discipline children, how to set limits, how to deal with anger and how to use words that work. A treatment study will now test the video and the workbook in 50 families.
- Many individuals, especially those with MRDD, ignore physical activity as an important aspect of daily life. A 35-minute prototype video provides beginner workouts to motivate individuals with MRDD to initiate a physical activity program effectively. This prototype led to a video-based instructional program for individuals with MRDD and their workout partners. The video includes a variety of exercises and encourages lifestyle changes and activities that help initiate and maintain physical activity. The program is currently in a clinical trial to determine its effectiveness as a motivational video.

ADVANCES IN PRENATAL DIAGNOSIS AND NEWBORN SCREENING

Support for advancing research on prenatal diagnosis and newborn screening has long been an imperative of the NICHD. For decades, mid-trimester amniocentesis and chorionic villus sampling (CVS) have remained prenatal diagnostic mainstays and obstetricians’ standard practice for at-risk pregnancies; however, work continues to advance these and other techniques in becoming safer and more effective. Over the past four years, the MRDD Branch has supported studies focused on developing non-invasive, safe, relatively inexpensive, and accurate techniques for prenatal diagnosis that practitioners can use during a woman’s first trimester of pregnancy.

Newborn screening has also moved to the forefront over the past few years, especially with the expansion of newborn screening panels that use tandem mass spectrometry. As with prenatal diagnosis, much work remains on how best to enhance the use and efficiency of newborn screening to reduce the morbidity and mortality of newborns who have or are at risk for heritable disorders.

Much of the MRDD Branch’s efforts in prenatal diagnosis research focus on developing non-invasive tests to determine fetal single-gene disorders, in particular, the potential for using fetal cells in maternal circulation to identify chromosomal aneuploidy. Unfortunately, significant

problems arose in trying to achieve the overall primary goals of these projects, mostly due to the scarcity of fetal cells in maternal blood. A number of grants within the MRDD Branch's prenatal diagnosis portfolio address these issues (see [Appendix C](#)).

In addition, the diversity in the MRDD Branch's newborn screening portfolio demonstrates the ever-expanding need to address a multitude of issues related to newborn screening—from improving the quality of blood-spot samples, to developing new screening assays for hyperbilirubinemia, FXS, and X-linked adrenoleukodystrophy.

Over the next four years, the NICHD, through the MRDD Branch, will enhance this initiative to encourage growth in the research field that takes advantage of technological advances encouraging the expansion of newborn screening programs. Please see [Appendix C](#) for grants within the MRDD Branch newborn screening portfolio.

EARLY AMNIOCENTESIS VERSUS LATE TRANSABDOMINAL CVS (EATA) TRIAL

This randomized trial assessed the safety and accuracy of amniocentesis and transabdominal CVS performed at 11 to 14 weeks of gestation, given that this time frame is increasingly relevant to early trisomy screening. The primary outcome measure was a composite of fetal loss plus preterm delivery before 28 weeks of gestation in cytogenetically normal pregnancies.

Amniocentesis at 13 weeks' gestation carries a significantly increased risk of *talipes equinovarus* (clubfoot) compared with CVS and suggested an increase in early, unintended pregnancy loss. The study²⁰ concluded that transabdominal CVS was a safer procedure than amniocentesis at 13 and 14 weeks' gestation, and that health care providers should not consider the latter before at least 14 weeks' gestation, and perhaps, not before 15 weeks' gestation.

An auxiliary study conducted in conjunction with this project demonstrated that first-trimester screening for Ts21 and Ts18 had good sensitivity, an acceptable false-positive rate, and compared in efficacy to second-trimester screening, based on maternal age, maternal levels of free beta human-chorionic gonadotropin, and pregnancy-associated plasma protein A, and on the measurement of fetal nuchal translucency. Thus, first trimester screening offers patients earlier and safer reproductive alternatives.

NICHD FETAL CELL ISOLATION STUDY (NIFTY)

NIFTY is a prospective, multi-center clinical project designed to develop non-invasive methods of prenatal diagnosis. The initial objective was to assess the utility of fetal cells taken from the peripheral blood of pregnant women for diagnosing or screening for fetal chromosome abnormalities. Researchers²¹ compared results from FISH analysis of interphase nuclei of fetal cells recovered from maternal blood to metaphase karyotypes of fetal cells obtained by amniocentesis or CVS. Better target-cell recovery and fetal-cell detection occurred with

²⁰ Philip, J., et al. (2004). *Obstetrics and Gynecology*, Jun;103(6), 1164-73.

²¹ Bianchi, D.W., et al. (2002). *Prenatal Diagnosis*, Jul;22(7), 609-15.

magnetic-based separation systems, such as magnetic-activated cell sorting (MACS), than with flow-sorting techniques, such as fluorescence-activated cell sorting (FACS). The sensitivity of aneuploidy detection using fetal-cell analysis from maternal blood compared well to single-marker prenatal serum screening; however, investigators must make technological advances before fetal-cell analysis has clinical applications as part of a multiple-marker method for non-invasive prenatal screening.

FIRST AND SECOND TRIMESTER EVALUATION OF ANEUPLOIDY RISK (FASTER) TRIAL

This multi-center prospective study compares the performance of first and second trimester methods of non-invasive screening for fetal aneuploidy, especially for Down syndrome. The FASTER study seeks to determine whether maternal serum levels of pregnancy-associated plasma protein A, free beta human-chorionic gonadotropin, or nuchal translucency size associate with certain obstetric complications. Findings²² include:

- Women with pregnancy-associated plasma protein A levels at or less than the 5th percentile were significantly more likely to experience spontaneous fetal loss at or before 24 weeks of gestation, in addition to low birth weight, preeclampsia, gestational hypertension, preterm birth and stillbirth, preterm premature rupture of membranes, and placental abruption.
- Nuchal translucency at or greater than the 99th percentile and free-beta subunit human chorionic gonadotropin at or less than the 1st percentile associated with an increased risk of spontaneous loss of pregnancy at or before 24 weeks of gestation.
- Low levels of pregnancy-associated plasma protein A during the first trimester strongly associated with a number of adverse pregnancy outcomes, and both low levels of free beta human-chorionic gonadotropin and large nuchal translucency associated with early fetal loss.

A number of additional projects have grown out of this preliminary study, including: evaluating nuchal translucent sonography as a screening test for cardiac malformations; measuring the accuracy of fetal echocardiography in diagnosing such malformations; and investigating the attitudes and preferences of women regarding prenatal screening and diagnosis. In the end, the FASTER trial plans to provide precise comparative data on how first trimester screening compares to second trimester screening, and on the optimal combination of screening tests for yielding the highest possible detection rate for Down syndrome, but with the lowest possible false-positive rate.

IDENTIFYING NEWBORNS WITH FRAGILE X SYNDROME (FXS)

The major goal of this planning grant is to design a large, multi-state study of infants with FXS and their families. Based on universal screening of 1,000,000 newborns, the study intends ultimately to determine the: incidence of FXS; ethical issues related to screening; effectiveness of different education and counseling models for families; attachment relationship between and among parents and children with FXS; and developmental patterns, and coping and adaptation patterns of affected families.

²² Dugoff, L., et al. (2004). *American Journal of Obstetrics and Gynecology*, Oct;191(4), 1446-51.

Critical to the success of this project is the identification of a reliable, valid, and cost-effective laboratory test to screen for FXS. Lack of such a test represents the real barrier in implementing this study. To overcome this barrier, researchers currently collaborate with two other projects to develop a technology that identifies all classes of FXS (both full-mutation and premutation, in both males and females).

In conjunction with this planning grant, the NICHD, through the MRDD Branch, and the National Human Genome Research Institute co-fund another project to conduct a pilot study to identify the ELSIs of implementing a major research project on FXS. Throughout the enrollment process for the FXS project, the pilot study team has begun to identify new, as well as recurring, issues related to informed consent, research staff training for handling disclosure issues, and other topics that arise from the large-scale FXS project.

FUTURE DIRECTIONS FOR THE MRDD BRANCH

OVERVIEW OF THE PROCESS

The MRDD Branch was the first NICHD component to conduct an expanded Branch report process and maintained a flexible approach to obtaining expert input during the portfolio review portion of the process. The nine members selected for the advisory panel collectively provided expertise in biomedical, behavioral, and biobehavioral research, including areas such as birth defects, basic and clinical neuroscience, clinical trials, international research, genetics, health disparities, training, legislation, and advocacy, as well as in ELSIs.

The Branch provided the panel with extensive background materials that summarized its activities and progress since the last report to the NACHHD Council. NICHD staff developed three overarching questions related to the scientific opportunities, public health issues, and research areas warranting greater or less emphasis for panel members' consideration and response (see [Appendix G](#) for the questions). The discussion spanned three conference calls, held on April 15, April 21, and May 10, 2005. During the first two calls, the experts responded to the three questions and engaged in open discussion among themselves. NICHD staff filled a peripheral role in the calls, answering questions if needed, but otherwise allowing the panel the opportunity for free discussion. During the last call, panel members responded to possible future directions Branch staff proposed, identified overarching themes from the previous calls, and evaluated the review process.

It is impossible to adequately capture the sizeable challenge that the panel members undertook. The Branch staff thank them for their patience with a new and changing process, for their thoughtfulness in addressing the questions posed, and for their helpfulness in achieving the goals. Their team spirit and team effort have set a high standard for this process in the future. Branch staff look forward to continuing the dialogue with willing members of the panel as progress toward realization of future directions for the Branch evolves over the next few years.

The Branch's own goals and priorities for its research focused on three main research/program areas—the MRDDRCs, autism research, and the NSRI—in addition to other aspects of the portfolio, such as research in Down syndrome, partnering with other Institutes and groups to further MRDD research, supporting meetings and conferences, and sponsoring research training.

FUTURE DIRECTIONS FOR THE MRDDRCs

The focus of the MRDDRC Program is to support researchers who aim to understand the causes of and to develop treatments for MRDD. The Centers' activities have increased this understanding dramatically. However, effective treatment remains difficult for a variety of reasons.

The fifth year hiatus in the competition of the MRDDRCs occurs in 2007, providing an opportune time to contemplate change. A tentative plan of action may include the following steps:

- Encourage the Centers' leaders to share unique resources, facilitate collaboration among users, and stimulate translation of knowledge about the causes of MRDD into interventions;
- Open the Program to co-funding by other NIH Institutes and Centers and government agencies to enhance funding of research areas addressed by the MRDDRCs;
- Solicit input from MRDDRC directors and their colleagues, patient advocacy groups, and potential funding partners to facilitate restructuring and continued vitality of the Program;
- Consider a formal evaluation of the P30 funding mechanism as a means to define and achieve new Program goals; and
- Update the Program guidelines and issue new guidelines that reflect contemporary Program goals.

FUTURE DIRECTIONS FOR AUTISM RESEARCH

Currently, the NIH supports a considerable number of projects in autism research. Networks of Centers, such as CPEA and STAART, are among these efforts. To maximize coordination and cohesion of NIH-sponsored efforts, the NIH is now considering the concept of a new Centers Program, *Autism Centers of Excellence (ACE)*, which will aim to avoid duplication, allow pooling and most efficient use of resources, and involve a larger number of investigators in autism research. This new initiative will encourage applications from investigators currently in the CPEA and STAART Networks, as well as from others who believe that they have sufficient expertise and resources to coordinate and implement a center or multi-site research program.

This initiative may also stipulate that:

- An individual may serve as principal investigator (or Center director) on only one application;
- The Center must focus on the causes of and best treatment for autism as listed in the Autism Research Matrix (see <http://www.nimh.nih.gov/autismiacc/CongApprCommRep.pdf> for more information about the research matrix);

- Both Centers and Networks may apply:
 - o Center applications should involve multidisciplinary research projects that incorporate an integrated theme; the research proposed must include at least one collaborative multi-site project or analysis of data collected previously from multiple sites.
 - o Network applications should involve multi-site projects with specific foci; the research may include one or more studies and should include studies and data from exemplar scientists in a particular field, who, together, can contribute to the field in ways each could not individually. For instance, several investigators may currently conduct imaging studies; they could use a multi-site network to combine and analyze the data from these existing studies, as well as, to collect new data using common standards.

FUTURE DIRECTIONS FOR THE NEWBORN SCREENING RESEARCH INITIATIVE (NSRI)

The NICHD focuses on identifying goals and proposed programs for the NSRI in areas of research that further the Institute's mission. To date, the NSRI has three areas of focus:

- Biomedical research
- Behavioral and social sciences research
- Infrastructure development

Based on these three areas of focus, the MRDD Branch proposes the following future directions to meet priority needs.

Biomedical Research

Within biomedical research, future Branch activities may include the following:

- Support the design and development of multiplexed screening assays for the expansion of newborn screening.
- Support research to:
 - o Improve dried blood-spot specimen collection, preparation, and storage;
 - o Investigate alternative types of specimens for use in newborn screening, including the effects of multiple variables, such as the volume and condition of the specimen, as well as appropriate times of collection for specific conditions;
 - o Investigate the appropriate mechanism(s) for storing residual blood spots to maintain their integrity; and
 - o Study the ELSIs surrounding the storage and usage of residual blood spots.
- Expand support for development and/or improvement of therapeutic interventions for genetic conditions detected through for newborn screening.
- Encourage studies on the natural history and biomarkers of specific genetic conditions, including long-term sequelae of those screened and treated; investigate the genotype/phenotype correlations and physiologic, metabolic, genetic, psychosocial, environmental, and behavioral factors related to genetic conditions suitable for newborn screening.
- Investigate clinical and ancillary service practices related to newborn screening and address

research to inform development of evidence-based standards that improve management of care for those children with conditions detected through newborn screening.

- Support basic research to determine the etiology (i.e., epigenetic, environmental, and genetic factors) of conditions that may be targets of screening in newborns.

Behavioral and Social Sciences Research

Within behavioral and social sciences research, future Branch activities may include the following:

- Investigate the psychological and social impact of false-positive and false-negative newborn screening results on children and their families—in particular, those newborns whose results are within the abnormal range, but who do not actually have a disease.
- Study the impact of newborn screening educational tools and resources on the behavioral practices of health care providers and on the health of their patients; develop a personal digital assistant (PDA)-based application that provides “ACT Sheet”-type information on screened conditions.
- Encourage research on ELSIs surrounding new technologies, using tandem mass spectrometry (also known as MS/MS) as a model; for instance, determine the potential social, behavioral, and economic challenges related to the identification of carriers of conditions represented on the array.

Infrastructure Development

In terms of infrastructure, future Branch activities may include the following:

- Encourage research that establishes standardized newborn screening program cut-off values and spectrum interpretation of analytes tested with MS/MS and other up-and-coming screening technologies, investigating challenges such as clinical heterogeneity and screening preterm infants.
- Support training of investigators and appropriate clinical providers in biochemical genetics.
- Play a secondary role to:
 - o Support studies on the cost-effectiveness of newborn screening that use economic modeling, including assessing opportunity, costs of the expansion of newborn screening, screening protocols, new technologies, and therapeutic interventions; and establish improved coding techniques for the use of health care services that relate to newborn screening.
 - o Support research on the use of information technology to support newborn screening activities, such as:
 - Developing large-scale data sharing through interpretation, reporting, tracking, and outcome evaluation, with the potential to interface the newborn screening system with electronic health records
 - Improving the newborn screening system infrastructure by developing computer algorithms to process data using statistically derived age-related cut-off values that initiate warning flags based on quantified disease-specific multi-analyte patterns
 - Continuing support of a workgroup of newborn screening specialists that provides recommendations on when testing should occur and what conditions should be included in panels for newborn screening

Partners

As the MRDD Branch pursues its goals in the NSRI, it may engage the following partners:

- Health Resources and Services Administration
- Centers for Disease Control and Prevention
- Food and Drug Administration
- National Institutes of Health
 - o Office of Rare Diseases (ORD)
 - o National Human Genome Research Institute (NHGRI)
 - o National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
 - o National Institute of Arthritis and Musculoskeletal Disorders (NIAMS)
 - o National Institute of Neurological Disorders and Stroke (NINDS)
 - o National Library of Medicine (NLM)
 - o National Institute on Deafness and Other Communication Disorders (NIDCD)
 - o National Institute of Mental Health (NIMH)
 - o National Center for Research Resources (NCRR)
 - o National Eye Institute (NEI)
 - o National Institute on Aging (NIA)
- U.S. Department of Defense
- Centers for Medicare and Medicaid Services
- Agency for Healthcare Research and Quality
- State Newborn Screening Programs/Laboratories
- Genetic Alliance
- March of Dimes
- American College of Medical Genetics
- Society for Inherited Metabolic Disorders

OTHER BRANCH FUTURE ACTIVITIES

Other future Branch activities may include the following items.

Possible Research Activities

- Coordinate trans-NIH efforts on Down syndrome.
 - o Bring multiple Institutes together to create and implement a matrix for issues on Down syndrome. Relevant institutes include, but are not limited to: NIA; NINDS; NEI; NIDCD; NIAMS; NHGRI; National Cancer Institute; National Heart, Lung, and Blood Institute; National Institute of Allergy and Infectious Diseases; and National Institute of Nursing Research, among others.
 - o Establish a research agenda for next five years with a matrix of questions to be answered on topics such as:
 - Aging and family dynamics
 - Consent when caregivers are impaired
 - Issues involving medications and clinical trial participation
 - Transitions to independent or assisted living for adults

- Co-morbid diagnostic issues
 - o Foster and encourage research programs that examine cascade or pathway contributions to:
 - Phenotypic features of Down syndrome, not just single-gene characteristics
 - Racial disparities in survival and access to care
- Team with NIA on aging issues for people with MRDD. This effort could focus on unique aspects of the aging process in the MRDD population, common problems, etc. The Surgeon General's report, *Closing the Gap: A National Blueprint to Improve the Health of Persons with Mental Retardation* (available at <http://www.nichd.nih.gov/publications/pubs/retardation.pdf>) might serve as a basis for a solicitation, or the Branch might convene a specific joint meeting to bring advocacy groups, caregivers, and researchers to a dialogue on these issues.
- Encourage research on the role of signaling pathways and transcription factors in the pathogenesis of MRDD conditions, such as Down syndrome or CdLS.
- Encourage research on the role of cholesterol and cholesterol metabolism in MRDD conditions, ranging from PKU to Smith-Lemli-Opitz syndrome, to gangliosidoses, to autism.
- Foster cross-disorder research that associates Down syndrome, FXS, and Rett syndrome, as well as PWS/AS and autism.
- Encourage studies to locate autosomal genes that cause MRDD. Technologies now exist to put large-scale, high-throughput screening within grasp and to permit evaluation of sufficient numbers of patients with idiopathic mental retardation for whom no diagnosis has yet been found, as well as appropriate control groups. Sufficient resolution of the human gene map, as well as gene maps of other organisms, exists to reveal areas of high degrees of synteny that make this approach feasible in the next five years.
- Encourage research on the roles of methylation, imprinting, and epigenetic factors in the pathogenesis of MRDD.
- Partner with the NIMH to look at co-morbid psychiatric conditions in children and adults with MRDD. This aspect of MRDD research is much neglected, but could now benefit from current pharmacologic and biobehavioral interventions. The NIMH has a PA to support single nucleotide polymorphisms (SNPs) research for obsessive-compulsive disorder and depression that is relevant to this future direction.
- Partner with the Pregnancy and Perinatology Branch of CDBPM at the NICHD to foster translational research in hypoxic/ischemic and very low birth weight children and in the use of ERPs to detect and monitor progress of brain development in these children.
- Encourage studies of very young children, particularly those at high risk for MRDD, using ERP and Magnetoencephalography (MEG). In the case of MEG, researchers might study pregnancies identified by prenatal diagnosis as high risk for developmental disabilities, possibly including baby siblings of children with autism, FXS, and Rett syndrome.
- Foster a program of intense research focus on first two years of postnatal development in humans from a multidisciplinary perspective. The first two years are often a time of "indecision" in the diagnosis of MRDD conditions and investigators have observed characteristics in retrospective studies. With the advent of the "thrust" toward newborn screening, the need to have firm understanding of what occurs during the first two years is critical. Studies that combine prospective ERPs, MEG, and behavioral, biobehavioral, and genetic studies could better define normative milestones and recognize abnormal signatures, thus providing non-invasive diagnostics that lead to earlier intervention.

- Encourage studies of sleep disorders and circadian rhythms in neurodevelopmental disorders. This pervasive problem for many families with children with MRDD has received relatively little research attention by the sleep research or MRDD research communities.
- Encourage studies of SIB in neurodevelopmental disorders. These efforts could be biomedical, behavioral, or biobehavioral studies that focus on mechanisms by which SIB arises in specific conditions, common pathways that may underlie the genesis of SIB, and interventions that reduce or redirect SIB in MRDD populations. Pharmacological interventions would also be of interest. Although multiple neurotransmitter systems have been implicated in SIB, the mechanisms by which these neurotransmitter systems affect SIB are still largely unknown.

Possible Conferences/Meetings

- Bring together MRDD researchers who focus on conditions that involve alterations in cholesterol homeostasis or cholesterol metabolism to determine the state-of-the-science for these conditions and their interconnections.
- Develop several meetings that focus on pre- and post-synaptic interactions, which occur among the various gene products affected by the combined syndromes, as well as on the role of methylation, etc., on function of specific chromosomal regions throughout the genome.
- Convene a meeting on the roles of methylation, imprinting, and epigenetic factors in the pathogenesis of MRDD, bringing together PWS/AS, Rett, Down, and other syndrome groups.
- Convene a meeting of developmental, behavioral, and biobehavioral scientists to focus specifically on brain development during the first two years of postnatal life in humans, and its equivalent developmental period in other primates. The meeting would bring together investigators who study developmental gene expression, those who study electrophysiology, neuroanatomy, imaging, etc., and those who study specific neurodevelopmental disorders with clinical manifestations during the first two years.
- Convene a meeting of researchers expert in sleep and sleep disorders, as well as those in the MRDD research community who study syndromes with particularly disturbed sleep patterns to determine the current status of knowledge about mechanisms by which such disorders arise in these populations. Sleep disorders are common among children and adults with MRDD, and the bases of the disorders may be in disrupted circadian rhythms, hypothalamic dysfunction, or aberrant melatonin homeostasis, among other causes.

Possible Training Activities

The MRDD Branch currently supports a number of training activities, which are listed in [Appendix D](#). The Branch may expand these activities to:

- Develop integrated interdisciplinary training programs for predoctoral and postdoctoral students in neurodevelopmental disorders. Programs would involve clinical experience for Ph.D. candidates and basic science training for M.D. students. Applicants could apply for one or both programs.
 - o The proposed postdoctoral training program plan might provide a variety of opportunities including:
 - Mentored research training in specific methods, disorders, and underlying pathogenetic mechanisms;

- A range of didactic experiences (including courses, seminars, and lectures) that integrate the study of clinical disorders, normal developmental processes, mechanisms of disease, and research methods; and
- Clinical exposures to complement previous levels of clinical experiences.
- o The predoctoral program would be unique and visionary in that it would integrate basic biomedical and biobehavioral sciences for multidisciplinary training in neurodevelopmental disorders, including strong training in bioinformatics and clinical trial design and execution.
- Encourage SBIR/STTR research for assistive technologies for individuals with MRDD, with a focus on facilitating interventions to enhance educational experiences for very young, preschool-, and elementary school-aged children. Tailoring the assistive-device experience to sensory modalities for which children with specific conditions have best receptive function is of great help to them. This effort would encourage device development and adaptation based on those observations.

FIGURES AND TABLES

FIGURE 1: RARE DISEASE COOPERATIVE RESEARCH CENTERS (RDCRCs)

1. Baylor College of Medicine*—Houston, TX
 - A. Baylor College of Medicine
 - B. University of Alabama, Birmingham
 - C. University of Florida College of Medicine
 - D. Children's Hospital of Boston
 - E. Greenwood Genetic Center
 - F. Children's Hospital
 - G. University of California Irvine Medical Center
2. Children's National Medical Center*—Washington, D.C.
 - H. Children's National Medical Center
 - I. Baylor University Medical Center
 - J. Children's Hospital of Philadelphia
 - K. Georgetown University
 - L. University of California, Cedar-Sinai Medical Center
 - M. Vanderbilt University Medical Center
 - N. Yale University Medical Center
 - O. Mount Sinai School of Medicine



FIGURE 2: FRAGILE X SYNDROME RESEARCH CENTERS (FXSRCs) AT THE MRDDRCs: “CENTERS-WITHIN-CENTERS”

1. University of Washington—Seattle, WA
A. University of Washington
B. University of California
2. University of North Carolina—Chapel Hill, NC
C. University of North Carolina
D. University of Kansas
3. Baylor College of Medicine—Houston, TX
E. Baylor College of Medicine
F. Emory University



FIGURE 3: STUDIES TO ADVANCE AUTISM RESEARCH AND TREATMENT (STAART) CENTERS

1. University of Washington—Seattle, WA
2. University of Rochester—Rochester, NY
3. Boston University Medical Campus—Boston, MA
4. Kennedy Krieger Research Institute, Inc.—Baltimore, MD
5. University of North Carolina—Chapel Hill, NC
6. Yale University—New Haven, CT
7. Mount Sinai School of Medicine of NYU—New York, NY
8. University of California, Los Angeles—Los Angeles, CA



TABLE 1: MRDD BRANCH PROJECTS BY SUPPORT MECHANISM, FISCAL YEAR 2004

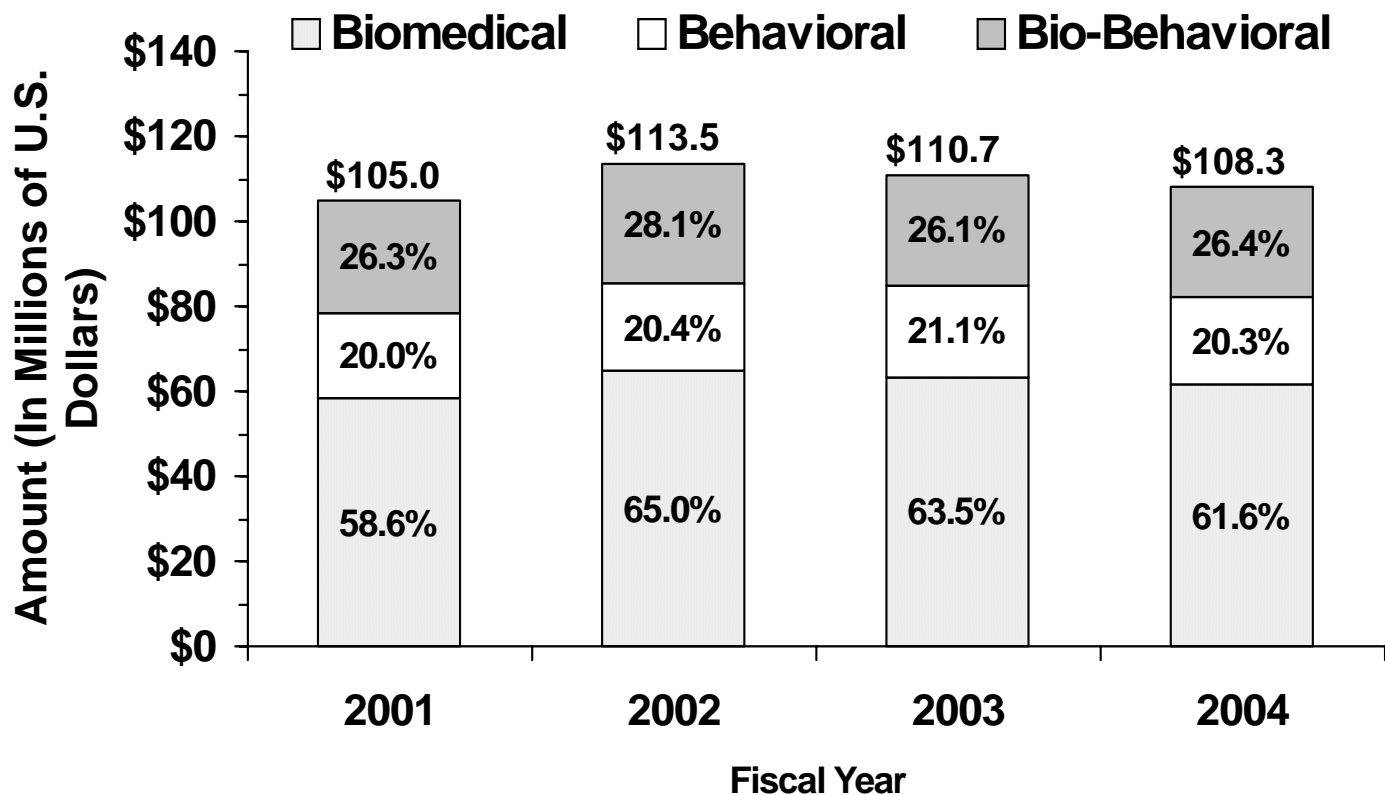
Support Mechanism	Number of Projects	Funds
Research Projects *	171	\$42,801,502
P01s	23	\$25,370,558
Research Centers **	16	\$20,701,397
Research Career Program	16	\$2,026,930
National Research Service Awards	6	\$208,058
Research Contracts	5	\$1,921,827
Training Programs	10	\$2,231,198
Cooperative Agreements ***	20	\$12,994,173
Totals	267	\$108,255,843

*R01, R03, R13, R21, R24, R37, R41, R42, R43 and R44

**P20, P30 and P50

***U01, U19 and U54

FIGURE 4: MRDD PROJECTS BY SUBJECT AREA, FISCAL YEAR 2001 THROUGH FISCAL YEAR 2004



**TABLE 2: MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES REVIEWS
IMPACT FACTORS**

Year	Impact Factor	Ranking In:			
		Clinical Neurology	Neurosciences	Pediatrics	Psychiatry
1999	0.795	89 (132)	144 (201)	36 (72)	55 (80)
2000	0.800	93 (201)	151 (201)	38 (71)	59 (82)
2001	1.442	53 (136)	119 (198)	19 (69)	49 (81)
2002	2.254	36 (138)	83 (197)	7 (68)	31 (88)
2003	3.479	15 (135)	46 (198)	3 (168)	17 (187)

Note: Numbers in parentheses are the total number of journals in the category.

FIGURE 5: MRDD BRANCH FUNDS BY SUPPORT MECHANISM, FISCAL YEAR 2004

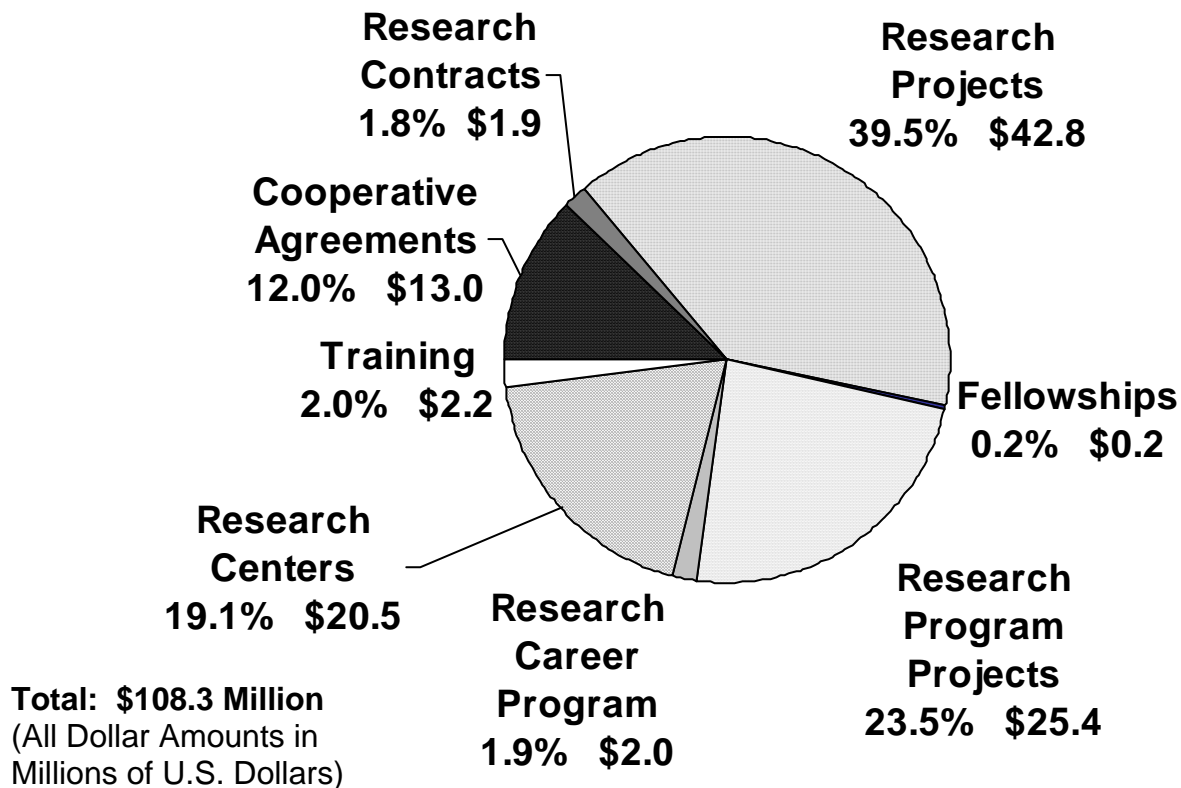


FIGURE 6: MRDD BRANCH FUNDS IN CURRENT AND CONSTANT DOLLARS, FISCAL YEAR 2001 THROUGH FISCAL YEAR 2004

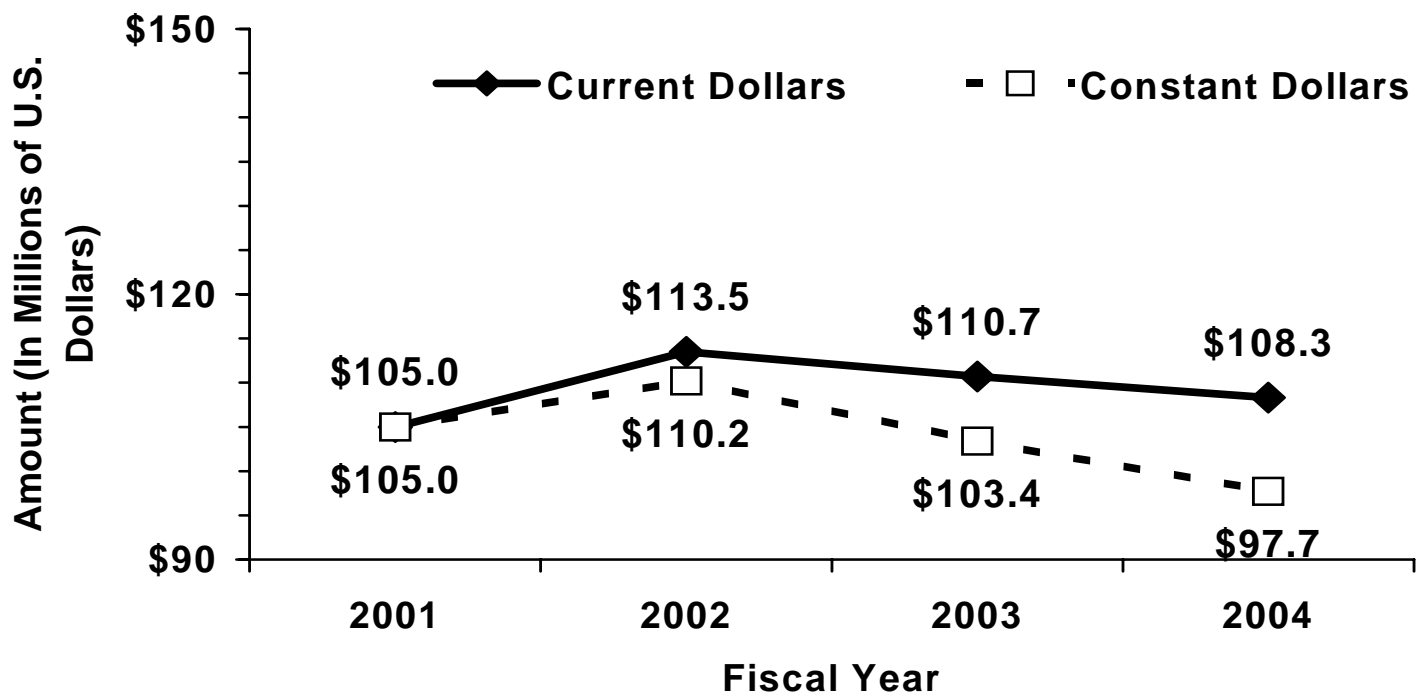


FIGURE 7: MRDD BRANCH FUNDING FOR SELECTED DISORDERS, FISCAL YEAR 2001 THROUGH FISCAL YEAR 2004

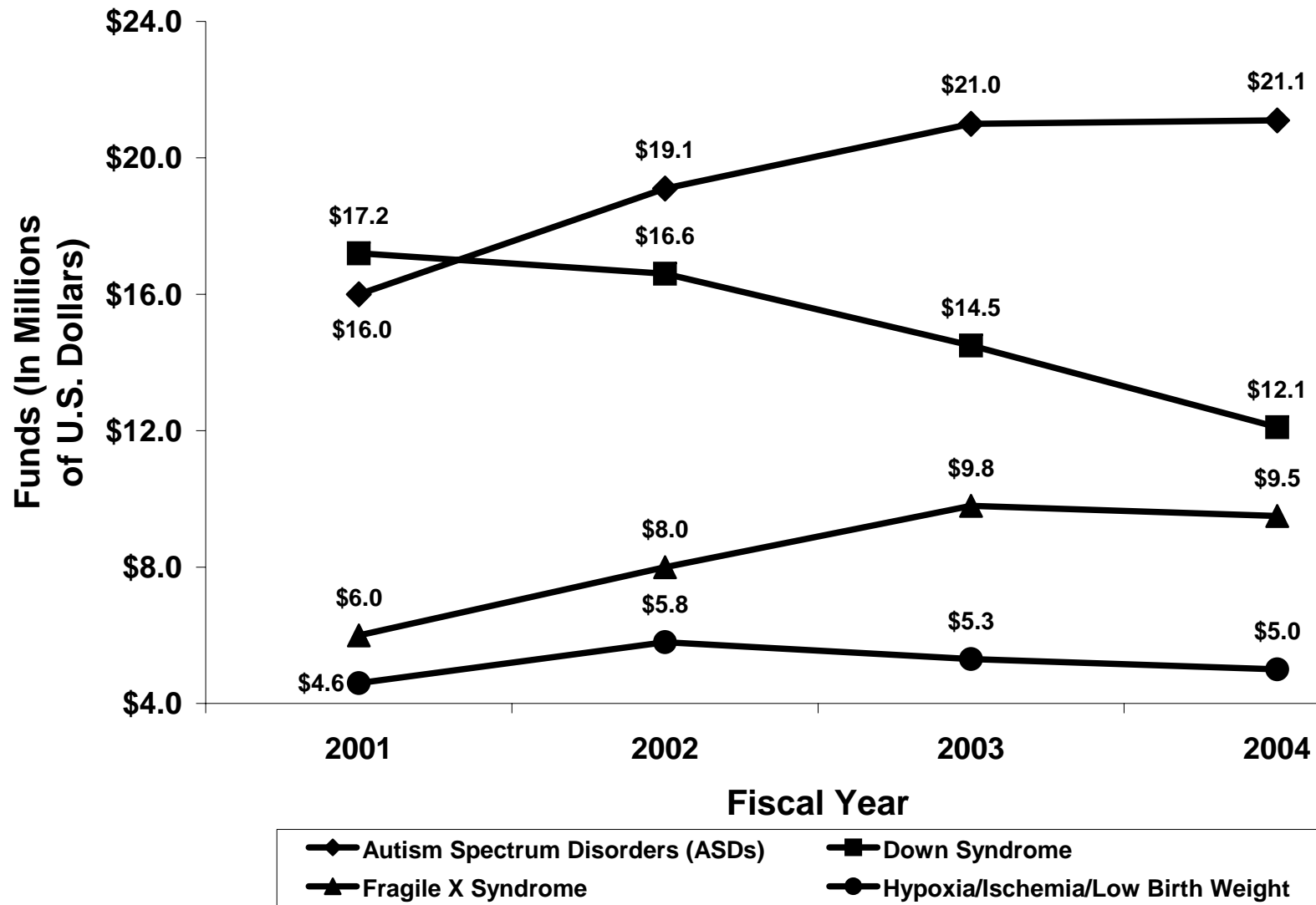


FIGURE 8: MRDD BRANCH FUNDING FOR SELECTED DISORDERS, FISCAL YEAR 2001 THROUGH FISCAL YEAR 2004

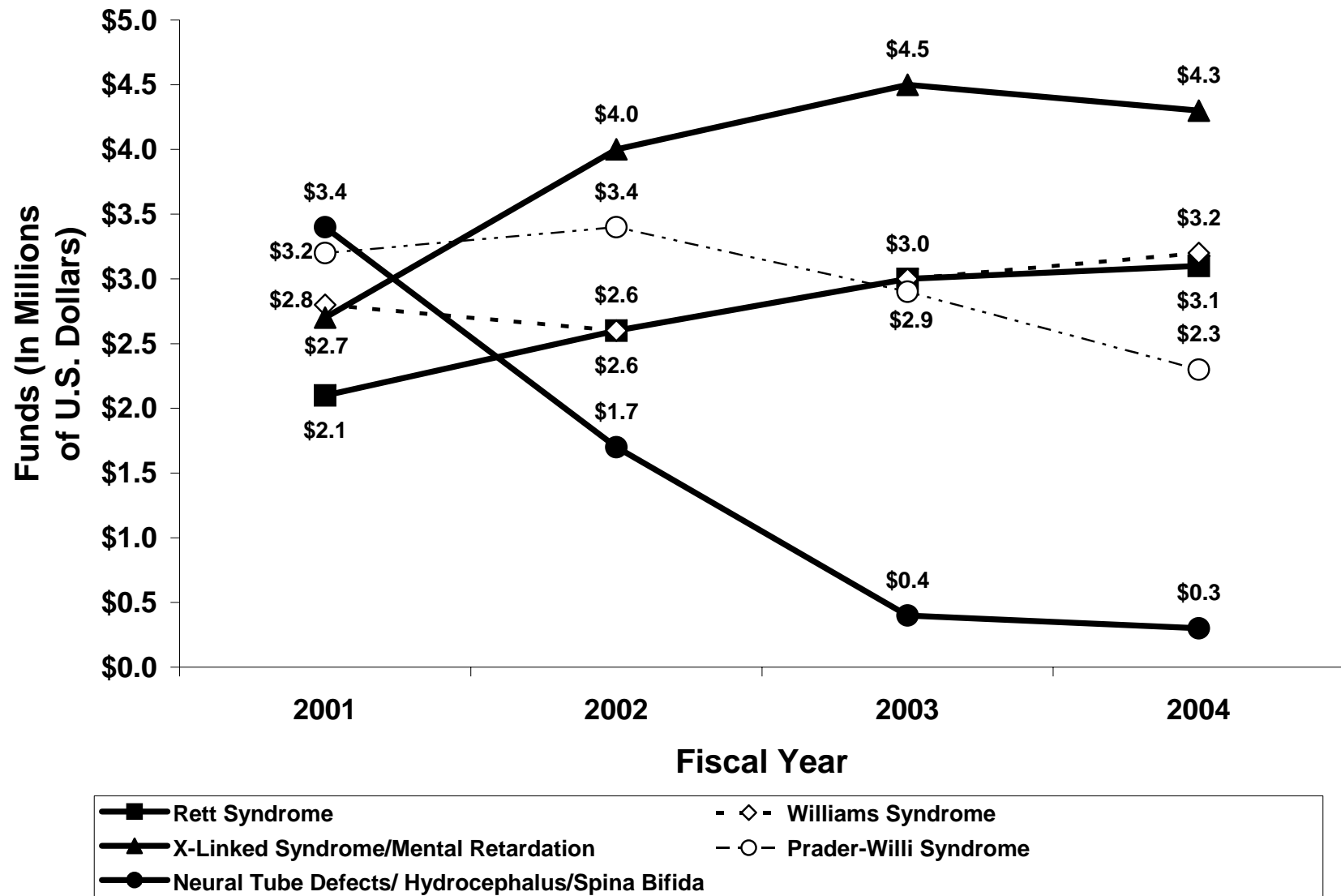
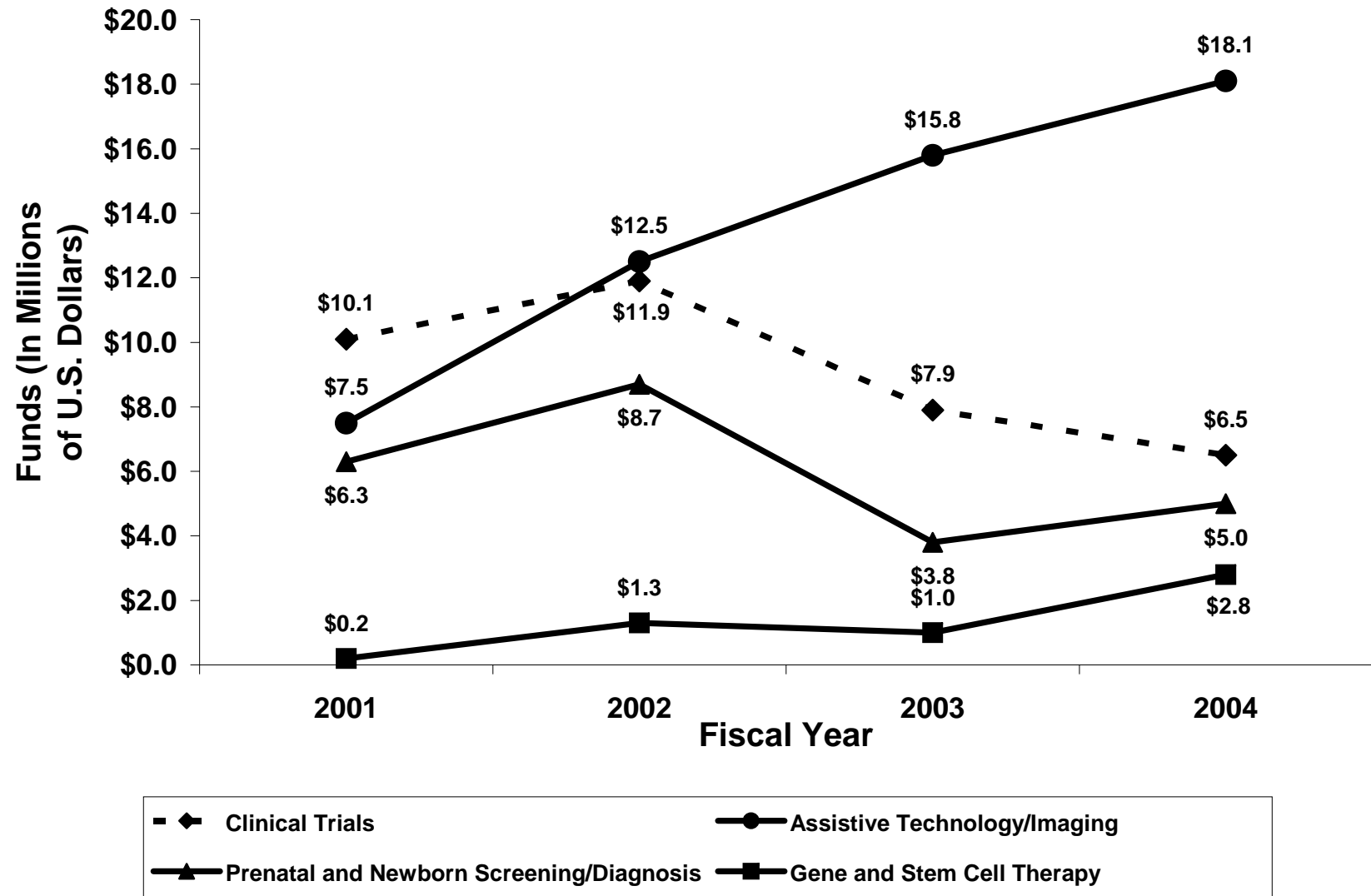


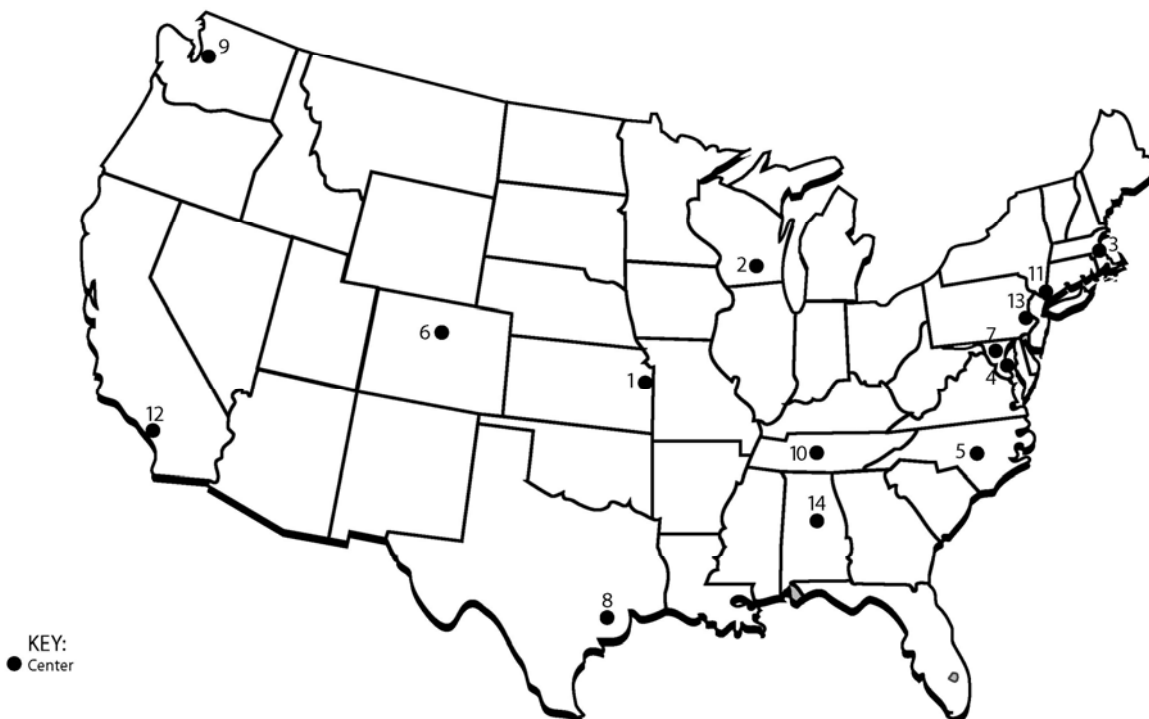
FIGURE 9: MRDD BRANCH FUNDING FOR SELECTED RESEARCH AREAS, FISCAL YEAR 2001 THROUGH FISCAL YEAR 2004



APPENDIX A: MRDD RESEARCH CENTERS (MRDDRCs) PROGRAM

The MRDDRC Program has Centers at the following locations.

- | | |
|--|---|
| 1. University of Kansas—Kansas City, KS | 8. Baylor College of Medicine—Houston, TX |
| 2. University of Wisconsin—Madison, WI | 9. University of Washington—Seattle, WA |
| 3. Children's Hospital—Boston, MA | 10. Vanderbilt University—Nashville, TN |
| 4. Children's National Medical Center—Washington, D.C. | 11. Albert Einstein College of Medicine—Bronx, NY |
| 5. University of North Carolina—Chapel Hill, NC | 12. University of California, Los Angeles—Los Angeles, CA |
| 6. University of Colorado—Denver, CO | 13. Children's Hospital of Philadelphia—Philadelphia, PA |
| 7. Kennedy Krieger Institute—Baltimore, MD | 14. University of Alabama—Birmingham, AL |



Vignettes about each MRDDRC, below, are meant to be illustrative, rather than comprehensive descriptions:

- **Alabama**—Civitan International Research Center, University of Alabama, Birmingham (UAB)—One of the newer MRDDRCs, this Center focuses on the following scientific areas: development, function, and plasticity of synapses; molecular biology/genetics of nervous system development and degeneration; neuroimmunoendocrinology and infectious diseases; and developmental disorders of non-neural organ systems.
- **California**—Neuropsychiatric Institute, University of California at Los Angeles—Now in its 34th year of funding, this Center focuses on cellular and molecular neuroscience and neurogenetics, systems neuroscience, clinical research, and socio-behavioral research and supports unique ethnographic studies of minorities. The facility's Fieldwork Training and Qualitative Data Core pioneered methods of transforming qualitative ethnographic data into

quantitative ethnographic data using software called *EthnoNotes FileMaker Program*, which Center researchers developed, and which is widely used by behavioral scientists both in the United States and abroad.

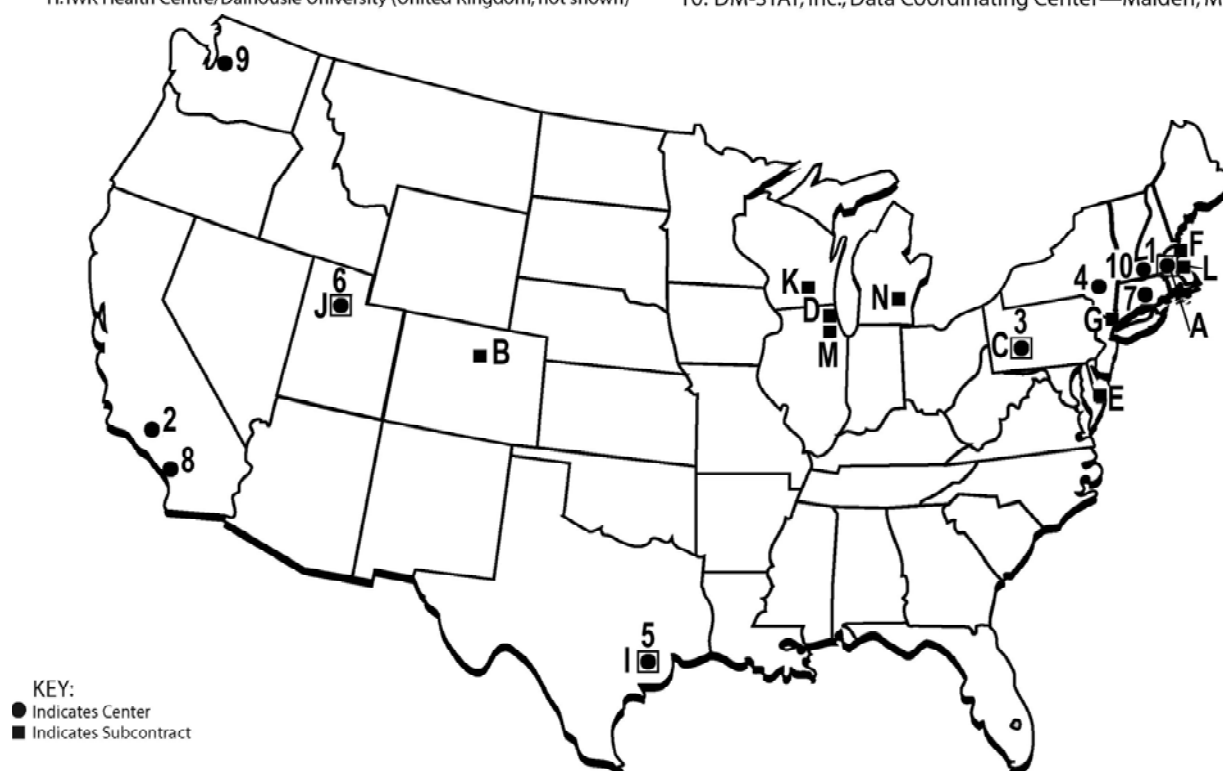
- **Colorado**—Department of Pediatrics, University of Colorado Health Sciences Center—Now in its 36th year of funding, the Center supports a broad range of studies that are conducted at most levels of biological organization, from molecules and cells to behavior; these efforts study several MRDD conditions and associated disorders, such as autism, inborn errors of metabolism, Down syndrome, FXS, and attention deficit/hyperactivity disorder.
- **District of Columbia**—Children’s National Medical Center—The newest of the 14 MRDDRCs, this Center encompasses four institutions in the Washington, D.C., area and collaborates with several other Centers. The MRDDRC supports investigations of autism, urea-cycle disorders, muscular dystrophy, epilepsy, and traumatic brain injury, among others.
- **Kansas**—University of Kansas, Lawrence—Research supported by this long-standing Center is very broad, but has a biobehavioral science focus that aims to develop interventions to help ameliorate MRDD. The cores support research in four thematic areas: language, communication disorders, and cognition; risk, intervention, and prevention; neurobiology; and cellular and molecular biology of early development.
- **Maryland**—Kennedy Krieger Institute, Inc.—This Center provides research services in: genetics (e.g., molecular genetics, cytogenetics, microarrays, and requisite bioinformatics); neuroscience (e.g., histology, imaging, and high-performance liquid chromatography); neuroimaging; and behavioral science. Some services are unique and service delivery is truly outstanding.
- **Massachusetts**—Children’s Hospital Corporation—This Center focuses on fostering collaborative interactions between basic and clinical scientists to advance understanding and treatment of many MRDD conditions, including periventricular leukomalacia, brain injury in infants with congenital heart disease, dyslexia, and cerebral cortical dysgenesis, among others. The Center’s affiliates, most of whom have dual appointments at Harvard Medical School, are clinicians and scientists who are advancing research in clinical domains underrepresented at other MRDDRCs.
- **New York**—Albert Einstein College of Medicine—Now in its 39th year of continuous funding, this Center supports studies in: normal and abnormal neural development, neuronal interactions, and the regulation and plasticity of synaptic transmission; systems neuroscience; pathobiology of developmental and degenerative disorders; neuroprotection and repair; and translational neuroscience. Neurophysiology (e.g., human and animal), tissue culture, morphology, imaging, and molecular/microarray cores support these studies.
- **North Carolina**—University of North Carolina (UNC) at Chapel Hill—This long-standing MRDDRC supports a broad research program that integrates and expands a portfolio of biobehavioral research projects on neurodevelopmental disorders such as autism, FXS, neurofibromatosis, and Turner syndrome, as well as support of basic biological and behavioral research relevant to MRDD conditions. Many Center affiliates collaborate closely in the contexts of the FXSRC, the STAART Center, and the Conte Center, all at UNC.

- **Pennsylvania**—Children’s Hospital of Philadelphia/University of Pennsylvania—Now in its 15th year, this Center supports more than 90 NIH-funded projects that cover a broad range of disorders including autism, urea-cycle disorders, neuroAIDS, etc. Basic neuroscience and genetics of MRDD conditions provide a strong focus. The cores facilitate study design and statistical analysis, molecular genetics, cellular neuroscience, and analytical neurochemistry. The Center, which encompasses two institutions in Philadelphia, engages in extensive collaborations with other appropriate centers, including several MRDDRCs.
- **Tennessee**—Vanderbilt University—Now in its 9th five-year funding cycle, this Center is one of the oldest in the Program. With strong institutional support, it focuses on four major scientific areas: communication and learning, developmental neurobiology and plasticity, mood and emotion, and family research. About half the Center’s investigators utilize model systems in basic research. The Center supports multidisciplinary studies of disorders, such as autism, PWS and WMS, aggression, attention deficit/ hyperactivity disorder, depression, anxiety, and learning disabilities.
- **Texas**—Baylor College of Medicine—This Center supports research in cellular and molecular aspects of brain development, genetic and epigenetic basis of diseases, inborn errors of metabolism, infectious diseases, autism, and other topics. The Center facilitates work on innovative technologies for diagnosis and screening of MRDD, methods to define clinical phenotypes, and clinical trials. The Center’s “ensemble of mouse cores” provides facilities and offers expertise for developing mouse models of MRDD.
- **Washington**—University of Washington, Seattle—Now in its 37th year of funding, the Center supports research in three domains: developmental and molecular genetics, developmental neuroscience and developmental processes, and behavioral science. Center affiliates collaborate in research on autism, craniofacial malformations, developmental toxicology, epilepsy, FXS, learning disabilities, neural plasticity, neurodegenerative disorders, and other topics. The scientific core facilities provide services in genetics, neuroscience, and behavioral science, as well as resources in the Infant Primate Research Laboratory and Instrument Development Laboratory.
- **Wisconsin**—University of Wisconsin, Madison—Affective processes that characterize individual-family-societal relations emerged as a major focus of this MRDDRC’s research, while research on molecular and genetic mechanisms of MRDD has also expanded. Alexander disease, DMD, Down syndrome, and FXS are among the disorders under intensive investigation at the Waisman Center. In addition, the Center offers several unique services, including its Research Participation Core, which contains a database that facilitates recruitment of special populations. A pharmaceutical laboratory that formulates candidate molecules into experimental drugs for nominal cost to the affiliates also falls into these unique services.

APPENDIX B: NETWORK ON THE NEUROBIOLOGY AND GENETICS OF AUTISM: COLLABORATIVE PROGRAMS OF EXCELLENCE IN AUTISM (CPEAs)

The CPEA Network has sites at the following locations.

1. Boston University—Boston, MA
A. Massachusetts General Hospital/Harvard University
2. University of California, Davis—Davis, CA
B. University of Colorado Health Sciences Center
3. University of Pittsburgh—Pittsburgh, PA
C. Carnegie Mellon University
D. University of Illinois, Chicago
4. University of Rochester—Rochester, NY
E. University of Delaware
F. Massachusetts General Hospital
G. Weill Medical College, Cornell University
H. IWK Health Centre/Dalhousie University (United Kingdom, not shown)
5. University of Texas Health Science Center—Houston, TX
I. Rice University
6. University of Utah—Salt Lake City, UT
J. Brigham Young University
K. University of Wisconsin
7. Yale University—New Haven, CT
L. McLean Hospital
M. University of Chicago
N. University of Michigan
8. University of California, Los Angeles—Los Angeles, CA
9. University of Washington—Seattle, WA
10. DM-STAT, Inc., Data Coordinating Center—Malden, MA



Each CPEA site supports a number of projects; some of these projects are described below:

- **Boston University**—Social-communicative abilities in autism; language delays and problems in autism; and brain pathology underlying social-communicative and language impairments in autism, using structural and functional magnetic resonance imaging
- **University of California, Davis**—Imitation and motor function in autism; measurement, predictors, clinical course, causes, and external validity of regression in autism; and longitudinal study of the developmental course of autism

- **University of California, Los Angeles**—How social, communication, and language deficits in autism start and develop; follow-up and extension of certain treatments for autism; phenotype and genotype in inversion and duplication of chromosome 15; and neuroimaging studies and deficits in social communication in autism
- **University of Pittsburgh**—Organizing information into concepts; visual perception and visual processing; sensory, motor, and executive problems; and functional brain imaging of language and cognition in persons with high-functioning autism and Asperger syndrome
- **University of Rochester Medical Center**—Animal models and mechanisms of injury in autism; behaviors that distinguish autism from other disorders; and mutations in genes involved in early development and their influences on gene function (research done in conjunction with the University of Rochester Medical Center’s Departments of Pediatrics and Neurology, the Hospital for Sick Children, in Toronto, Cornell Medical College, and the U.S. Environmental Protection Agency)
- **University of Utah**—Genetics and genetic susceptibility of autism; brain development; and serotonin function and immune system functioning in autism
- **University of Washington**—Relationships between the brain and behavior in autism; language problems characteristic of autism; early diagnosis of autism and resulting outcomes; neuroimaging studies of autism; and the genetics of autism
- **Yale University**—Genetics of persons with autism; genetics of persons with autism and Asperger syndrome, their families, and family members with related disorders; changes to the nervous system in autism; behavior problems, epilepsy, and puberty in adolescents with autism; and regression studies to define the phenomena, predict outcomes, and evaluate medical factors that may play a role, such as vaccines, seizures, and prenatal conditions
- **University of Texas Health Science Center at Houston (Affiliated Program)**—Development of communication and social behavior and its relationship to brain function in autism; abnormalities in brain structure related to autism; and animal studies of brain structure, injury, and behavior

**APPENDIX C: MRDD BRANCH SOLICITATIONS,
FISCAL YEAR 2001 THROUGH FISCAL YEAR 2005**

**REQUEST FOR APPLICATIONS (RFAs), NOTICES (NOT), AND PROGRAM ANNOUNCEMENTS
(PAS, PARS, TPAs) FUNDED OR CO-FUNDED BY THE MRDD BRANCH**

- TPA-01-077—Strategies for Germ-line Modification in the Rat
- RFA-HG-02-005—Large Scale Genotyping for the Haplotype Map of the Human Genome
- RFA-NS-02-007—Gene Therapy for Neurological Disorders
- RFA-HD-02-009—Fragile X Syndrome Research Centers (FXSRCs) Program
- NOT-HD-02-015—Network on the Neurobiology and Genetics of Autism: Collaborative Programs of Excellence in Autism (CPEA) Data Coordinating Center
- TPA-02-172—Novel Genetic Methods to Map Functional Neuronal Circuits and Synaptic Change
- RFA-AR-03-001—Muscular Dystrophy Collaborative Research Centers (MDCRCs) Program
- RFA-AR-03-002—Developmental Planning Grants for MDCRCs
- RFA-MH-03-005—Autism Research Centers of Excellence: The Studies to Advance Autism Research and Treatment (STAART) Program
- PAR-03-007—Novel Genetic Methods for Mapping Functional Neuronal Circuits
- RFA-TW-03-007—Brain Disorders in the Developing World: Research Across the Lifespan
- RFA-RR-03-008—Rare Disease Clinical Research Network
- RFA-HD-03-027—Mental Retardation and Developmental Disabilities Research Centers (MRDDRCs) Program
- PA-03-097—Basic and Clinical Research on Rett Syndrome and *MECP2*
- TPA-03-129—Research on the Psychopathology of Intellectual Disabilities (Mental Retardation)
- RFA-TW-04-001—International Bioethics Education and Career Development Awards
- RFA-AR-04-008—MDCRCs Program Reissue
- NOT-OD-04-008—Exploratory Centers (P20) for Interdisciplinary Research
- RFA-RM-04-015—Training for a New Interdisciplinary Workforce
- RFA-HD-04-024—MRDDRCs Program Reissue

- PA-04-050—Ethical, Legal, and Social Implications (ELSI) Regular Research Program
- PA-04-051—ELSI Small Grants (R03) Program
- PA-04-085—Research on Autism and Autism Spectrum Disorders (ASDs)
- RFA-MH-05-007—Identifying Autism Susceptibility Genes
- PAS-05-024—Basic and Clinical Research on Rett Syndrome and *MECP2*
- PA-05-038—Muscular Dystrophy: Pathogenesis and Therapies
- RFA-HD-05-024—MRDDRCs Program Reissue
- PA-05-051—Mentored Clinical Investigator Career Development Awards in Muscle Disease Research
- PA-05-052—Ruth L. Kirschstein National Research Service Awards for Postdoctoral Fellowships in Muscle Disease Research
- PA-05-053—Trans-Disciplinary Muscle Diseases Workshops
- PA-05-100—Brain Disorders in the Developing World: Research Across the Lifespan
- PA-05-108—Shared Neurobiology of Fragile X Syndrome and Autism

Possible solicitations for the upcoming fiscal year:

- Innovative Therapies and Tools for Screenable Disorders
- Translational Research on Developmental Brain Disorders

APPENDIX D: TRAINING GRANTS CURRENTLY SUPPORTED BY THE MRDD BRANCH

HD043704—Minority Predoctoral Fellowship

GRANTEE: ACRA, CAROLINE; UNIVERSITY OF MIAMI, CORAL GABLES, FLORIDA

SPONSOR: MUNDY, PH.D., PETE

The primary aims of this research proposal are to evaluate long-term effectiveness of intervention programs of different intensity on cognitive, language, and behavior development, and to assess the degree to which the benefits of early intervention are maintained three to four years after the completion of the assigned program.

HD041889—Disability Predoctoral Fellowship

GRANTEE: RAINEY, ROBERT; UNIVERSITY OF CALIFORNIA, LOS ANGELES, CALIFORNIA

SPONSOR: COUREY, ALBERT

The specific aim of this research is to study mitochondrial biogenesis with a focus on how defects in the mitochondrial intermembrane space protease (IMMP2L) may result in disease, specifically Tourette's syndrome.

HD08250—Disability Predoctoral Fellowship

GRANTEE: RYTTER, KRISTIN; UNIVERSITY OF WASHINGTON, SEATTLE, WASHINGTON

SPONSOR: DALE, PHILIP

This project directly addresses the question of how parents perceive and respond to the functioning of handicapped and able-bodied children, specifically studying the teaching practices of mothers who have a mentally retarded, physically disabled, or able-bodied child.

HD041255—Minority Predoctoral Fellowship

GRANTEE: VALDOVINOS, MARIA; UNIVERSITY OF KANSAS, LAWRENCE, KANSAS

SPONSOR: SCHROEDER, STEPHEN

The intent of this study is to develop a systematic method for collecting and monitoring adverse side effects of psychotropic medication in people with developmental disabilities living in community settings.

HD046337—Postdoctoral Fellowship

GRANTEE: BEAN, LORA, J.H. ; EMORY UNIVERSITY, ATLANTA, GEORGIA

SPONSOR: SHERMAN, STEPHANIE

The primary aims of this research are to identify environmental exposures and genetic variants on chromosome 21 that contribute to congenital heart defect susceptibility. The study will use a candidate gene approach in a Down syndrome population that has complete atrioventricular septal defects.

HD044361—Postdoctoral Fellowship

GRANTEE: GABEL, LISA ANN; BROWN UNIVERSITY, PROVIDENCE, RHODE ISLAND

SPONSOR: FALLON, PH.D., JUSTIN

The primary aim of this research is to characterize the mechanisms that regulate the activity-dependent translation and degradation of FMRP.

HD008692—Postdoctoral Fellowship

GRANTEE: HETH, JASON; UNIVERSITY OF IOWA, IOWA CITY, IOWA

SPONSOR: DAVIDSON, BEVERLY

This project seeks to determine if one can achieve correction of mucopolysaccharidosis VII through the use of adeno-associated viral vector 5 containing beta glucuronidase.

HD042346—Postdoctoral Fellowship

GRANTEE: O’HEARN, KIRSTEN; JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

SPONSOR: LANDAU, BARBARA

The aim of this grant is to develop a functional imaging study to determine if individuals with Williams syndrome have damage in their ability to use a “spatial pointer” to locate and track objects.

HD043614—Postdoctoral Fellowship

GRANTEE: ROPER, RANDALL; JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

SPONSOR: REEVES, ROGER

The purpose of this research is to generate a mouse model with trisomy and monosomy for regions on mouse chromosome 10 that are homologous to human chromosome 21, specifically segmental trisomic (Ts2Rhr) and monosomic (Ms2Rhr) mice, which will be compared with human clinical data.

HD042921—Postdoctoral Fellowship

GRANTEE: VON KOCH, CORNELIA; UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, SAN FRANCISCO, CALIFORNIA

SPONSOR: FARMER, DIANA

The aim of this grant is to utilize a sheep model of surgically created hindbrain myelomeningocele to determine if it is possible, via fetal surgery, to prevent hindbrain herniation and hydrocephalus formation.

HD042269—Independent Scientist Award

GRANTEE: MALKOVA, LUDISE; GEORGETOWN UNIVERSITY, WASHINGTON, D.C.

COLLABORATORS—GALE, KAREN; GIEDD, JAY; AND MOTT, STEPHEN

The primary aim of this research is to investigate the role of amygdale and its specific subdivisions for socio-emotional behavior and to identify the critical periods and neural triggers for developmental abnormalities in an animal model of autism.

HD01179—Independent Scientist Award

GRANTEE: MCCAFFERY, PETER; SHRIVER CENTER, WALTHAM, MASSACHUSETTS

The primary aim of this research is to map the pathways of retinoid metabolism in the developing central nervous system.

HD044716-01—Mentored Clinical Scientist Development Award

GRANTEE: BELL, MICHAEL; CHILDREN'S NATIONAL MEDICAL CENTER, WASHINGTON, D.C.

MENTOR: GALLO, VITTORIO

ADVISORS: HOFFMAN, ERIC; NATALE, JOANNE

This project seeks to characterize the role of TNF-alpha in damage to oligodendrocytes; the work will use tissue culture and transgenic mice that lack TNF receptors the expression of genes involved in the inflammatory cascade.

HD041400-01—Mentored Clinical Scientist Development Award

GRANTEE: DALY, THOMAS; UNIVERSITY OF ALABAMA, BIRMINGHAM, ALABAMA

MENTOR: CURIEL, DAVID

ADVISORS: PONNAZHAGAN, SELVARANGAN; PEREBOEV, ALEXANDER; AND FALLON, MICHAEL

This effort seeks to improve efficiency of adeno-associated virus targeting of the liver to increase the effective dose of vector delivered, and to decrease unwanted extra-hepatic transduction, using AAV5 as the targeting moiety.

HD001359-01—Mentored Clinical Scientist Development Award

GRANTEE: FOLLETT, PAMELA; CHILDREN'S HOSPITAL, BOSTON, MASSACHUSETTS

MENTORS: JENSEN, FRANCES; VOLPE, JOSEPH

This project will study the time course and cellular specificity of immature oligodendrocytes injury in the developing brain, the presence and subtype composition of glutamate receptors on oligodendrocytes during periods of vulnerability, and the effects of glutamate agonists and antagonists on white-matter injury and development.

HD040848-01—Mentored Clinical Scientist Development Award

GRANTEE: HICKEY, ROBERT; UNIVERSITY OF PITTSBURGH, PITTSBURGH, PENNSYLVANIA

MENTOR: GRAHAM, STEVE

ADVISOR: KOCHANNEK, PATRICK

This work uses tissue culture and gene knockout technology to investigate potential mechanisms of COX-2 toxicity, particularly the possibility that COX-2 and nitric oxide synthase act synergistically to form peroxynitrite.

HD001396—Mentored Clinical Scientist Development Award

GRANTEE: MCQUILLEN, PATRICK; UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, SAN FRANCISCO, CALIFORNIA

SPONSOR: FERRIERO, DONNA

COLLABORATORS: STRYKER, MICHAEL; SHATZ, CARLA

The overall goal of this research is to investigate the subplate neurons of the developing rat cerebral cortex as a model of hypoxic ischemic brain injury in the newborn.

HD001384—Mentored Clinical Scientist Development Award

GRANTEE: SAHIN, MUSTAFA; CHILDREN'S HOSPITAL, BOSTON, MASSACHUSETTS

SPONSOR: GREENBERG, MICHAEL

The goal of this project is to characterize the signaling pathways that regulate synaptogenesis in the developing brain.

HD40321—Mentored Clinical Scientist Development Award

GRANTEE: SOBIN CHRISTINA A.; ROCKEFELLER UNIVERSITY, NEW YORK, NEW YORK

OVERSEEING SPONSOR: KARAYIORGOU, MARIA

RESEARCH SPONSOR: POSNER, MICHAEL

SPONSORS: GEYER, MARK A.; PICKEL, VIRGINIA M.; AND GILBERT, CHARLES D.

The primary aim of this research is to compare 22q11DS children and matched normal controls with regard to efficiency of three attention networks, pre-pulse inhibition, and neuropsychological functioning, temperament, and behavior.

HD01174—Mentored Clinical Scientist Development Award

GRANTEE: WANG, PAUL PRINCETON; UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PENNSYLVANIA

SPONSOR: GUR, RUBEN C.

CONSULTANTS: RESCORLA, LESLIE A.; HASELGROVE, JOHN C.

The primary aim of this research is to examine the neuropsychological structure of working memory, its neurobiological foundations, and its relationship to other cognitive processes.

HD046541—Mentored Patient-Oriented Research Career Development Award

GRANTEE: ARNOLD, GEORGIANNA; UNIVERSITY OF ROCHESTER, ROCHESTER, NEW YORK

MENTORS: BENNETTO, LIOSA; KAHLER, STEVEN; KLORMAN, FAFANEL; OAKES, DAVID; PEARSON, THOMAS; AND SZILAGYI, PETER

This project plans to acquire didactic instruction in clinical research skills, as well as familiarity with the fundamentals of cognition and neuropsychology, and to complete a mentored clinical research study on attentional dysfunction (such as attention deficit/hyperactivity disorder) among children with PKU.

HD043179—Mentored Patient-Oriented Research Career Development Award

GRANTEE: KEREN, RON; CHILDREN'S HOSPITAL OF PHILADELPHIA, PHILADELPHIA, PENNSYLVANIA

MENTORS: BHUTANI, VINOD K.; SCHATZ, J. SANFORD

COLLABORATOR: CNAAN, AVITAL

The primary aim of this research is to develop a simple and practical clinical prediction rule that pediatricians and neonatologists can use to predict term and near-term newborns' risk of developing severe neonatal hyperbilirubinemia after discharge from the hospital.

HD043112—Mentored Patient-Oriented Research Career Development Award

GRANTEE: LEVY, BRYNN; MOUNT SINAI SCHOOL OF MEDICINE/NEW YORK UNIVERSITY, NEW YORK,

NEW YORK

SPONSOR: HIRSCHHORN, KURT

CO-MENTOR: WETMUR, JAMES

The primary aim of this research is to test the hypothesis that whole genome amplification of single cells will provide enough representative DNA for successful aneuploidy screening by conventional and DNA array comparative genomic hybridization analysis.

HD048502—Mentored Patient-Oriented Research Career Development Award

GRANTEE: RAUEN, KATE; UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, SAN FRANCISCO, CALIFORNIA

SPONSOR: ALBERTSON, DONNA G.

CO-SPONSORS: MCCORMICK, FRANK; EPSTEIN, CHARLES J.; AND HOYME, H. GENE

The primary aim of this research is to test the hypothesis that, due to the phenotypic similarity to Noonan syndrome and neurofibromatosis-1, patients with Costello syndrome have a congenital/constitutional alteration in the Ras pathway.

HD047713—Mentored Patient-Oriented Research Career Development Award

GRANTEE: SICES, LAURA; CASE WESTERN RESERVE UNIVERSITY, CLEVELAND, OHIO

SPONSOR: DROTAR, DENNIS

MENTORS: GLASCOE, FRANCES; HACK, MAUREEN; KELLEHER, KELLY; SCHLUCHTER, MARK; TAYLOR, H. GERRY; AND STANGE, KURT

CONSULTANTS: HENEGHAN, AMY; MANOS, MELISSA; AND SIMON, CHRIS

The primary aims of this research are to identify factors that affect the delivery of preventive developmental services by primary care physicians, and to develop an innovative intervention that improves the detection and initial management of developmental delays in young children.

HD040843—Mentored Patient-Oriented Research Career Development Award

GRANTEE: SUTTON, VERNON REID; BAYLOR COLLEGE OF MEDICINE, HOUSTON, TEXAS

MENTOR: BEAUDET, ARTHUR

The primary aim of this research proposal is to test the hypothesis that the phenotypic features associated with maternal or paternal uniparental disomy are the result of over-expression or absence of expression of an imprinted gene or genes on chromosome 14.

HD01361—Midcareer Investigator Award in Patient-Oriented Research

GRANTEE: DRISCOLL, DANIEL J.; UNIVERSITY OF FLORIDA, GAINESVILLE, FLORIDA

The primary aims of this research are to genetically and clinically dissect the imprinted genes underlying each component of PWS, and to explore the potential role that early childhood morbid obesity plays in mental retardation.

HD046712-01A1—Midcareer Investigator Award in Patient-Oriented Research

GRANTEE: GLASS, IAN; UNIVERSITY OF WASHINGTON, SEATTLE, WASHINGTON

This work will evaluate candidate genes that may play a causative role for an overlapping or allelic disorder, disease-associated chromosomal rearrangements, and/or integrated phenotyping

and genetic mapping in cerebellar developmental disorders utilizing consanguineous pedigrees.

HD001380-05—Midcareer Investigator Award in Patient-Oriented Research

GRANTEE: PIAZZA, PH.D., CATHLEEN; KENNEDY KRIEGER RESEARCH INSTITUTE, BALTIMORE, MARYLAND

The primary aim of this research is to apply the functional analysis method to assessing and treating SIB and feeding disorders to determine the contributions of environmental events in developing and maintaining these problems.

HD40761-01—Mentored Quantitative Research Career Development Award

GRANTEE: MENON, VINOD; STANFORD UNIVERSITY, PALO ALTO, CALIFORNIA

MENTOR: REISS, ALLAN

COLLABORATORS: GLOVER, GARY; KRAEMER, HELENA C.

The primary aim of this research is to study a process of protracted functional maturation of fronto-parietal neural networks involved in the development of working memory in order to gather new findings about the neural bases of the development of higher cognitive processes in children and adolescents.

HD007489-11—Postdoctoral Training in Mental Retardation Research

PRINCIPAL INVESTIGATOR (PI): ABBEDUTO, LEN; WAISMAN CENTER, UNIVERSITY OF WISCONSIN, MADISON, WISCONSIN

Training in this program revolves around the behavioral, biobehavioral, and social sciences in MRDD with an emphasis on social-affective, communication, and family processes. This program has four key elements: 1) mechanisms of coordinating and monitoring individualized training experiences for each trainee; 2) intensive research training experiences; 3) participation in core curriculum of seminars; and 4) completion of tangible “products.”

HD007032-26—Training Program in Mental Retardation and Developmental Disabilities

PI—DE VELLIS, JEAN; UNIVERSITY OF CALIFORNIA, LOS ANGELES, CALIFORNIA

The objective of this program is to train young investigators whose careers will focus either on MRDD research *per se*, and/or on solving basic problems in growth and development that relate to MRDD.

HD007105-26A1—Training Program in Mental Retardation and Developmental Disabilities

PI—DESNICK, ROBERT; MOUNT SINAI SCHOOL OF MEDICINE, NEW YORK, NEW YORK

This training program provides combined basic science and clinical background in the etiology, pathophysiology, prevention, and treatment of diseases leading to MRDD. The training is primarily in the fields of genetics and biochemical genetics, with specific subdisciplines in molecular and biochemical genetics, developmental neurobiology, neurogenetics, cytogenetics, and clinical genetics.

HD07149-28—Training Program in Genetics and Genomics of Human Disease

PI—LIFTON, RICHARD (FORMERLY: DiMAIO, DANIEL); YALE UNIVERSITY SCHOOL OF MEDICINE, NEW

HAVEN, CONNECTICUT

The objective of this training program is to mentor students interested in using genetic and genomic approaches to understand the pathophysiology of human disease, with a focus on the study of model systems for genetic, biochemical, and developmental pathways. The main methods used are positional cloning of human and mouse disease genes, complemented by bioinformatics and computational analysis, transgenic and knockout methods in mouse, as well as use of model organisms including *Drosophila*, *C. elegans*, and yeast to define biochemical pathways and permit genetics screening for modifier loci.

HD007473-11—Training Program in Mental Retardation/Developmental Disabilities

PI—MUNDY, PETER; UNIVERSITY OF MIAMI, CORAL GABLES, FLORIDA

This program focuses on development of knowledge concerning psychosocial risk factors associated with developmental disabilities, especially those endemic to children raised in poverty. Although there is a strong concentration possible in autism, the main emphasis is on understanding lesser degrees of retardation and disabilities including: learning disabilities, mild mental retardation, and language delay. Multidisciplinary training ranges from the use of epidemiological methodology to quantify risk and risk reduction, to the development of new techniques for early identification of children with developmental disabilities and the development of new intervention approaches for ameliorating the effects of multiple risk factors, biological and social insults to development, and the assessment of developmental disabilities and those at high risk for these developmental problems.

HD040127-04—Postdoctoral Research in Neurodevelopmental Disorders

PI—PIVEN, JOSEPH; UNIVERSITY OF NORTH CAROLINA/CHAPEL HILL, CHAPEL HILL, NORTH CAROLINA

The purpose of this training program is to help researchers develop expertise in both the biological basis and clinical manifestations of neurodevelopmental disorders.

HD007226-27—Behavioral Research Training in Developmental Disability

PI—WALDEN, TEDRA; VANDERBILT UNIVERSITY, NASHVILLE, TENNESSEE

The purpose of this program is to train behavioral scientists who are committed to research on mental retardation and other developmental disabilities. The program is characterized as interdisciplinary and involves both predoctoral and postdoctoral trainees.

HD007306-18

PI—NAGGERT, JURGEN; JACKSON LABORATORY, BAR HARBOR, MAINE

This two-week annual short course in Medical and Experimental Mammalian Genetics provides comprehensive exposure to the latest advances in both theoretical and practical genetics, with a focus on attracting bright young professionals to the field of genetic research and teaching.

In addition, the MRDD Branch has supported the following institutional training grants:

- Research Training in Mental Retardation—Department of Psychology, University of Notre Dame, Notre Dame, Indiana. John Borkowski, Director—Supported through 2004, currently in no-cost extension.
- Mental Retardation Research Training in Psychology—Case Western Reserve University, Cleveland, Ohio. Douglas Detterman, Director—Supported through 2005, currently beginning no-cost extension.
- Training in Human and Medical Genetics—Case Western Reserve University, Cleveland, Ohio. Terry Hassold, Director (new director to be appointed)—Supported through 2004, currently in no-cost extension.
- Interdisciplinary Research Training in MRDD—University of Kansas, Lawrence, Kansas. Kathryn Saunders, Director—Supported through 2005, currently beginning no-cost extension.

APPENDIX E: MRDD BRANCH PERSONNEL

Gilian Engelson, M.P.H., joined the MRDD Branch as a health scientist administrator in December 2004 to assist Dr. Rodney Howell[€] with the development of NICHD's NSRI, and to assist in managing MRDD grants and contracts related to newborn screening. Ms. Engelson received her bachelor's degree in biology from the University of Michigan-Ann Arbor and her master's of public health, with a focus on public health genetics, from Columbia University. Most recently at the Maternal and Child Health Bureau, Health Resources and Services Administration (HRSA), she served as a program officer within the Genetic Services Branch, where she managed grants for the Sickle Cell Disease and Newborn Screening Programs, and the newly funded Regional Genetics and Newborn Screening Collaboratives, while also providing administrative assistance to the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. Prior to her position at HRSA, Ms. Engelson worked at the American Cancer Society, Planned Parenthood, and the March of Dimes.

James Hanson, M.D., joined the MRDD Branch in 2002, as chief, after holding various positions at DHHS, the CDC, and, most recently, the NCI. After receiving his M.D. from the University of Iowa College of Medicine, he completed his internship and residency in pediatrics at the Johns Hopkins Hospital. His research interests include birth defects epidemiology, prenatal and neonatal screening, and public health/policy aspects of genetics, preventive health care, and children's health, to name a few. He is a past-president of the Teratology Society and was a founding fellow/member of the Board of Directors of the American College of Medical Genetics. Dr. Hanson moved out of the MRDD Branch in 2003 to serve as acting director of the newly established CDBPM. In 2005, he was appointed CDBPM director.

Alice Kau, Ph.D., joined the MRDD Branch as a health scientist administrator in June 2003. Dr. Kau is responsible for the extramural activities in the Branch's Biobehavioral Research Program. She also serves as a key member of the autism and behavioral science research communities on behalf of the Branch and assists in formulating and planning activities of these programs. Dr. Kau received her doctorate degree in developmental psychology from Ohio State University and completed a postdoctoral fellowship in clinical psychology at the Department of Pediatrics at the Johns Hopkins University School of Medicine. Prior to coming to the NICHD, Dr. Kau was an assistant professor/psychologist at the Kennedy Krieger Institute, Johns Hopkins University.

Mary Lou Oster-Granite, Ph.D., joined the MRDD Branch as a health scientist administrator in July 1999. A long-time grantee of the NICHD, Dr. Oster-Granite served as a tenured professor of biomedical sciences at the University of California before joining the Branch. As a developmental neuroembryologist, neurovirologist, and neurogeneticist, her research interests include genetic models of MRDD, and most recently, animal models of Down syndrome and ornithine carbomyl transcarbamylase deficiency. Her programmatic interests include brain function at a cellular/molecular level, developmental neurobiology, neurochemistry, neurovirology, molecular genetics, and gene therapy. Since May 2003, Dr. Oster-Granite has served as acting, currently temporary, Branch chief.

[€] Dr. Howell, a former member of the NACHHD Council, now provides expert guidance for the Institute's NSRI.

Ljubisa Vitkovic, Ph.D., joined the Branch as a health scientist administrator in January 2003. Dr. Vitkovic manages the MRDDRC Program and is responsible for research in the areas of neuroscience, including neurotoxicology and other environmental effects on neurodevelopment. Dr. Vitkovic has an M.S. degree in nuclear physics and a doctorate degree in biophysics from Michigan State University. Prior to joining the NICHD, he worked for the NIMH, NIAID, and NINDS, all at the NIH. He was also a professor for the French Academy of Sciences in Montpellier, France, and most recently a private consultant. Dr. Vitkovic has published more than 50 peer-reviewed scientific articles and edited several books. He serves on the editorial boards of *Molecular Psychiatry* and *NeuroImmunoModulation*.

**APPENDIX F: BRANCH-SPONSORED MEETINGS AND CONFERENCES,
FISCAL YEAR 2001 THROUGH FISCAL YEAR 2005**

- Gene Therapy for Neurological Disorders—Parkinson Disease and Lysosomal Storage Diseases, Rockville, Maryland, October 23-24, 2000
- Banbury Conference on Fragile X Syndrome (FXS), Cold Spring Harbor, New York, March 4-7, 2001
- Mental Retardation and Developmental Disabilities Research Centers (MRDDRCs) Directors' Meeting, Charleston, South Carolina, March 7-8, 2001
- Gatlinburg Conference, Riverside, California, March 17-20, 2001
- NIH Autism Coordinating Committee Meeting with National Autism Advocacy Groups, Bethesda, Maryland, March 30, 2001
- *Workshop on Chromosome 18: State of the Science*, Bethesda, Maryland, May 17-18, 2001
- International Prader-Willi Syndrome Scientific Meeting, St. Paul, Minnesota, June 27-29, 2001
- Surgeon General's Call for Action on Health Disparities and Mental Retardation Meeting, Bethesda, Maryland, July 12, 2001
- Haplotype Map Meeting, Washington, D.C., July 17-18, 2001
- NIH Autism Coordinating Committee Scientific Conference: *Potential Cellular and Molecular Mechanisms in Autism and Related Disorders*, Jointly sponsored by members of the NIH Autism Coordinating Committee, Bethesda, Maryland, September 6-7, 2001
- MRDDRCs Directors' Meeting, Bethesda, Maryland, November 1-2, 2001
- *Surgeon General's Listening Session on Health Disparities and Mental Retardation*, Bethesda, Maryland, October 10, 2001
- *Mental Health Aspects of FXS*, Rockville, Maryland, November 16-17, 2001
- Interagency Autism Coordinating Committee—Inaugural Meeting, Bethesda, Maryland, November 19, 2001
- *Emotional and Behavioral Health in Persons with Mental Retardation/Developmental Disabilities: Research Challenges and Opportunities*, Jointly Sponsored by the NICHD, National Institute of Neurological Disorders and Stroke, the National Institute of Mental Health, the NIH Office of Rare Diseases, and the Joseph P. Kennedy Jr., Foundation, Rockville, Maryland, November 29-December 1, 2001
- *Surgeon General's Meeting on Health Disparities and Mental Retardation*, Georgetown

University School of Medicine, Washington, D.C., December 5-6, 2001

- Gatlinburg Conference, *NIH 101*, Annapolis, Maryland, March 14-16, 2002
- FXS Investigators' Meeting, Potomac, Maryland, March 25-26, 2002
- Banbury Conference on FXS, Cold Spring Harbor, New York, April 7-10, 2002
- *International Conference on Maternal Phenylketonuria (PKU): New Developments and the Need for New Strategies*, Bethesda, Maryland, April 11-12, 2002
- Interagency Autism Coordinating Committee—Biennial Meetings, Bethesda, Maryland, May 24 and November 22, 2002
- *Symposium on Gene Therapy for the Mucopolysaccharidoses*, American Society of Gene Therapy Meeting, Boston, Massachusetts, June 7, 2002
- MRDDRCs Directors' Meeting, Madison, Wisconsin, June 16-18, 2002
- High Risk/Baby Sibling Autism Research Conference, Sponsored by the NICHD and the National Alliance for Autism Research, Washington, D.C., June 19-20, 2002
- Collaborative Programs of Excellence in Autism (CPEA) Researchers' Annual Meeting, Washington, D.C., July 23-24, 2002
- Planning Workshop on Relating Genetic Variation and Health, Bethesda, Maryland, August 8, 2002
- NIH Autism Coordinating Committee Scientific Conference: *Research on Psychosocial and Behavioral Interventions in Autism: Confronting the Methodological Challenges*, Jointly sponsored by members of the NIH Autism Coordinating Committee, Rockville, Maryland, September 5-6, 2002
- *10th International Conference on Chromosome 21 and Down Syndrome*, Barcelona, Spain, September 26-29, 2002
- *International Symposium on Lysosomal Storage Diseases*, Baltimore, Maryland, October 14-15, 2002
- MRDDRCs Directors' Meeting, Bethesda, Maryland, October 28, 2002
- FXS Mouse Model Meeting, JAX Laboratories, Bar Harbor, Maine, January 15-17, 2003
- *Sharpening the Tools: Current Status and Future Directions for the Use of Fetal Cells and Nucleic Acids from Maternal Blood for Prenatal Diagnosis*, Bethesda, Maryland, January 23-24, 2003
- Gatlinburg Conference, Annapolis, Maryland, March 20-22, 2003
- Banbury Conference on FXS, Cold Spring Harbor, New York, March 29-April 2, 2003
- Meeting on Cognitive Function in Down Syndrome, Denver, Colorado, April 3-6, 2003

- CPEA Researchers' Annual Meeting, Los Angeles, California, May 12-14, 2003
- Interagency Autism Coordinating Committee—Biennial Meetings, Bethesda, Maryland, May 13 and November 21, 2003
- MRDDRCs Directors' Meeting, Washington, D.C., June 9, 2003
- *Coalition for Children's Health*, Chevy Chase, Maryland, July 16, 2003
- *Symposium on Challenging Behavior in CHARGE Syndrome*, Cleveland, Ohio, July 25-27, 2003
- FXS Investigators' Meeting, Rockville, Maryland, August 7-8, 2003
- High Risk/Baby Sibling Autism Research Conference, Sponsored by the NICHD and the National Alliance for Autism Research, Washington, D.C., August 18, 2003
- *Translation of Neuroscience Research Into Effective Interventions*, Baltimore, Maryland, September 4, 2003
- Rare Disease Collaborative Research Centers Directors' Meeting, Children's National Medical Center, Washington, D.C., September 29-30, 2003
- Muscular Dystrophy Cooperative Research Centers (MDCRCs) Directors' Conference, Bethesda, Maryland, October 8-9, 2003
- *Glutamic Acid Decarboxylase and Batten Disease Workshop*, Bethesda, Maryland, November 13-14, 2003
- MRDDRCs Directors' Meeting, Bethesda, Maryland, November 17-18, 2003
- *Autism Summit Conference: Developing a National Agenda*, Jointly sponsored by members of the NIH Autism Coordinating Committee, Washington, D.C., November 19-20, 2003
- *Human Glycosylation Disorders 2003*, San Francisco, California, December 3, 2003
- FXS Newborn Screening Board, Bethesda, Maryland, December 4, 2003
- MDCRCs Steering Committee Meeting, Bethesda, Maryland, January 5, 2004
- Synthesis Conference on Newborn Screening for FXS, Palm Springs, California, February 2-4, 2004
- Williams Syndrome Conference, San Diego, California, February 5, 2004
- Sensory Processing Disorders Conference, Boulder, Colorado, February 6-8, 2004
- *Infant and Child Neurotoxicity Studies*, Honolulu, Hawaii, February 10-14, 2004
- *Collaborative Genetic Disease Research: Need/Opportunity*, Annual Meeting, Orlando, Florida, March 3-7, 2004

- Gatlinburg Conference: *Research and Theory in Intellectual and Developmental Disabilities*, San Diego, California, March 2004
- *University of California, Davis, Epilepsy and Autism Conference*, Old Town Sacramento, California, March 2004
- National Center on Birth Defects and Developmental Disabilities Conference, Washington, D.C., July 26-28, 2004
- NIH Funding Opportunities for Junior Investigators, Children's Research Institute, Children's National Medical Center, Washington, D.C., April 1, 2004
- Banbury Conference on FXS, Cold Spring Harbor, New York, April 25-28, 2004
- *Symposium on Autism*, International Meeting for Autism Research (IMFAR) Annual Meeting, Sacramento, California, May 7-8, 2004
- Interagency Autism Coordinating Committee—Biennial Meetings, Bethesda, Maryland, May 11 and November 19, 2004
- CPEA/Studies to Advance Autism Research and Treatment (STAART) Annual Meeting, Washington, D.C., May 17-20, 2004
- Hershey Conference on Developmental Brain Injury, Pacific Grove, California, June 9-13, 2004
- Chromosome 21 Experts Meeting, Tysons Corner, Virginia, June 11-14, 2004
- *State of the Science: FXS Research*, Washington, D.C., June 23, 2004
- FXS Investigators' Meeting, Washington, D.C., June 24, 2004
- Cornelia de Lange Syndrome Scientific Symposium and 22nd National Meeting, Chicago, Illinois, June 24-27, 2004
- *World Congress of Chromosomal Abnormalities*, San Antonio, Texas, June 28-June 30, 2004
- *At the Crossroads: Common Pathways in Fragile X and Autism*, Jointly sponsored by the NICHD, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, and the Fragile X Research Foundation, Salve Regina University, Newport, Rhode Island, July 7-8, 2004
- MRDDRCs Directors' Meeting, Bethesda, Maryland, July 12-13, 2004
- *Coalition for Children's Health*, Chevy Chase, Maryland, July 14, 2004
- High Risk/Baby Sibling Autism Research Conference, Sponsored by the NICHD and the National Alliance for Autism Research, Washington, D.C., August 11-12, 2004
- FXS Newborn Screening Steering Committee Meeting, Washington, D.C., September 28, 2004

- NIH Workgroup on Newborn Screening, Bethesda, Maryland, September 8, 2004
- NIH Funding Opportunities for Junior Investigators, MRDDRC at Kennedy Krieger Institute, Baltimore, Maryland, October 7, 2004
- Brain Disorders Network and International Clinical, Operational and Health Services Research Training Award (ICOHRTA) Investigators' Meeting, Bethesda, Maryland, October 12-14, 2004
- MRDDRCs Directors' Meeting, Bethesda, Maryland, November 8, 2004
- *Integrating the Clinical and Basic Sciences of Autism: A Developmental Biology Workshop*, Ft. Lauderdale, Florida, November 11-14, 2004
- MDCRCs Review, Washington, D.C., December 9-10, 2004
- Burden of Disease Workshop, Bethesda, Maryland, January 26-27, 2005
- National Human Genome Research Institute Centers of Excellence in ELSI Research Program Meeting, Bethesda, Maryland, February 3-4, 2005
- *Down Syndrome: Toward Synaptic Function and Cognition*, North Bethesda, Maryland, February 13-15, 2005
- Banbury Conference: *Translational Approaches to FXS*, Cold Spring Harbor Laboratory, New York, February 28-March 2, 2005
- *Collaborative Genetic Disease Research: Need/Opportunity*, Annual Meeting, Dallas, Texas, March 2005
- Gatlinburg Conference, Annapolis, Maryland, March 17-19, 2005
- High Risk/Baby Sibling Autism Research Conference, Sponsored by the NICHD and the National Alliance for Autism Research, Bethesda, Maryland, March 31-April 1, 2005
- *Premature Ovarian Failure and FXS*, Potomac, Maryland, April 14-15, 2005
- *Symposium on Autism*, IMFAR Annual Meeting, Boston, Massachusetts, May 5-7, 2005
- *David W. Smith Workshop on Malformations/Morphogenesis*, Iowa City, Iowa, August 6-7, 2005

In addition, the MRDD Branch supported the following scientists at relevant meetings: Dawson—*9th International Congress of Neuronal Ceroid Lipofuscinosis*, 2003; Gutmann—*Neurofibromatosis*; Levitt—*Developmental Neurogenomics*; Finkelstein—*FASEB Summer Conference on Folate, B12, and 1C Metabolism*; Schwartzkroin—*Seizures and Autism*; and Pessah—*Annual Autism, Genes, and Environment Conference*.

APPENDIX G: QUESTIONS TO THE EXPERT PANEL

OVERARCHING QUESTION 1

Given its mission, what are the most important scientific opportunities that the MRDD Branch should try to pursue in the next four years?

In answering Question 1, please consider:

- What areas of scientific research in the Branch portfolio are undergoing the most rapid advances or appear best poised for seminal discoveries in the next four years?
 - o How should the Branch prioritize research, training, clinical, and related requirements of the Newborn Screening Research Initiative among themselves and with other Branch priorities?
 - o Should the Branch direct resources to help integrate neuroscience knowledge across all levels of biological organization from subcellular to behavioral?
- Of these areas, which ones need special action/stimulation by the MRDD Branch? What form should that action take?
- What infrastructure enhancements will be needed to support these research priorities?

OVERARCHING QUESTION 2

What are the most important public health issues, concerning the population that the MRDD Branch serves, that need to be addressed in the next four years?

In answering Question 2, please consider:

- Given that the scientific disciplines related to intellectual and developmental disabilities are extremely diverse and new resources precious, how can the Branch focus its efforts to foster an overall portfolio whose research advances benefit the largest number of intellectually disabled persons possible?
- How can the Branch most efficiently and effectively stimulate and facilitate the translation of basic research findings into clinical and community practice?
- With whom should the Branch partner in this endeavor?

OVERARCHING QUESTION 3

What areas deserve less emphasis because progress has been made or will continue without further stimulation from the NICHD in general and the MRDD Branch in particular?

**APPENDIX H: DISEASES AND SYNDROMES: MRDD BRANCH
RESEARCH SUPPORT FOR FISCAL YEAR 2004**

- N-Acetylglutamate synthetase deficiency (NAGS)
- Adenylsuccinase deficiency
- Adrenoleukodystrophy
- Agammaglobulinemia
- AIDS dementia
- Alexander disease
- Allen-Herndon-Dudley syndrome
- Angelman syndrome
- Arginase deficiency (argininemia)
- Arginosuccinate lyase deficiency (arginosuccinic aciduria)
- Arginosuccinate synthetase deficiency (citrullinemia)
- Asperger syndrome
- Autism
- Bardet-Biedl syndrome
- Barth syndrome
- Batten disease
- Bilirubinemia
- Canavan disease
- Carbamyl phosphate synthetase (CPS) deficiency
- Cerebral Hemorrhage (Very Low Birth Weight infants)
- Cerebral Palsy
- Charcot-Marie-Tooth syndrome
- CHARGE syndrome
- Chromosome 1q syndrome
- Chromosome 18q- syndrome
- Citrullinemia, type II
- Coffin-Lowry syndrome
- Cornelia de Lange syndrome
- Costello syndrome
- Craniosynostosis
- CRASH
- Cystic fibrosis
- DiGeorge syndrome
- Down syndrome
- Duchenne/Becker muscular dystrophy
- Epilepsy
- Fetal alcohol syndrome
- Fragile X syndrome
- Fascioscapulohumoral dystrophy
- Gangliosidoses

- Gaucher disease
- Glutaric acidemia I
- Glutaric acidemia II
- Glycerol kinase deficiency
- Holoprosencephaly
- Homocystinuria
- Hurler syndrome
- Hyperammonemia
- Hyperornithinemia (HHH) syndrome
- Hypothyroidism
- Hypoxic-ischemic encephalopathy
- Incontinentia pigmenti
- Kabuki syndrome
- Kearns-Sayre Syndrome
- Krabbe disease
- Lead Toxicity
- Leigh syndrome
- Lesch-Nyhan syndrome
- Lissencephaly
- MLS syndrome
- Malnutrition
- Alpha-Mannosidosis
- MELAS syndrome
- MERRE syndrome
- MERRF syndrome
- Mohr-Tranebjaerg syndrome
- MNGIE syndrome
- Mucopolysaccharidosis type VII
- Myotonic dystrophy
- Neural Tube Defects
- Neurofibromatosis 1 and 2
- Niemann-Pick Disease Type A
- Organic Acidemias
- Ornithine Transcarbamylase (OTC) deficiency
- Otocephaly
- Peroxisomal disorders
- Phenylketonuria
- Prader-Willi syndrome
- Propionic acidemia
- Refsum disease
- Rett syndrome
- Roberts syndrome
- Retinitis pigmentosa
- Saethre-Chotzen syndrome

- Smith-Magenis syndrome
- Smith-Lemli Opitz syndrome
- Snyder-Robinson syndrome
- Spinocerebellar ataxia
- Tardive dyskinesia
- Tay Sachs disease
- Tourette syndrome
- Turner syndrome
- Velocardiofacial syndrome
- Von Recklinghausen's syndrome
- WAGR syndrome (Wilms Tumor)
- Wiskott-Aldrich syndrome
- X-linked disorders
- Zellweger syndrome