The IDDRC@WUSTL was selected to host the annual National Directors meeting of the 14-center network of IDDRCs in November 2017. This two-day meeting was attended by over 50 people, including NIH Program staff, Center leaders, and clinical-translational core faculty. The meeting served as a catalyst for several important new IDDRC network initiatives:

1. A half-day clinical genetics workshop highlighted models for personalized clinical genetics and the interface between personalized medicine, pathogenicity determination, and translation of potential biomarkers in animal models. The WUSTL Human Genomic Characterization Unit was featured as one model for accruing and analyzing genetic data through a clinical genetics pipeline with St. Louis Children’s Hospital.

2. Several IDDRCs engaged in the development of patient-specific induced Pluripotent Stem Cells (iPSCs) and presented the challenges in refining and standardizing protocols across laboratories. An NIH-led workgroup was initiated to create synergies across laboratories in the network, with IDDRC@WUSTL investigator Dr. Kristen Kroll serving as a co-chair.

3. A half-day breakout session for clinical-translational core leaders addressed the challenges of informatics across programs and generated strategies for leveraging the Clinical and Translational Sciences Award Programs (CTSAs), which are colocated at most member institutions. Since the meeting, a grant application has been developed to improve interpretation of clinical genomic information in patients across IDDRCs through data collection and integration with electronic health records and ClinGen.

4. The March of Dimes Prematurity Research Centers, some of which are co-located within IDDRC institutions, presented scientific progress and additional ways to leverage this cohort of pregnant mothers.

5. The UCEDD (University Centers for Excellence in Developmental Disabilities), and LEND (Leadership Education in Neurodevelopmental and Related Disabilities) programs, many of which are co-located within IDDRC institutions, offer opportunities for training and disseminating information to families and clinicians. Centers highlighted successful aspects of these partnerships, as well as areas for further enhancements.

BY THE NUMBERS
YEAR 3 PROGRESS REPORT
98 Member Investigators
63 Scientific Publications
13 New Federal Research Awards

Administrative Core

Model Systems Core
- Cellular Models
- Neurophysiology
- Animal Behavior

Faculty Navigator
- Basic Sciences
- Clin-Trans Sciences

Developmental Neuroimaging Core
- Data Acquisition
- Data Analysis

Clinical-Translational Core
- Human Genomic Characterization
- Developmental and Behavioral Assessment
“Midnight Scan Club” Develops High-Fidelity Individual Connectome Maps

A group led by IDDRC investigator Nico Dosenbach ran brain scans late at night (when scanner charges are lowest) to collect large amounts of data in individual brains.

Conventionally, relatively small amounts of neuroimaging data are collected in many individuals and the data are analyzed by averaging across brain scans of groups of people. The focus of the midnight scan club study, in contrast, was to collect large amount of data in small number of individuals and to examine individual-level functional brain networks using resting state functional MRI and functional activation MRI in response to cognitive tasks such as reading. This individual-connectome approach revealed new types of spatial and organizational variability in brain networks, including unique network features and topologies that corresponded with structural and task-derived brain features. Recognizing variations in neural processing across different individuals may help neurologists understand and treat brain disorders such as seizures or help to understand why people respond uniquely to different drug treatments.

The study data suggest that precision individual connectomics may serve as model for examining the organization of typical and atypical individual human brains.

IBIS Network: New Links to Autism and Early Brain Development

The Infant Brain Imaging Study (IBIS) Network, a collaboration of four IDDRCs (University of Washington, UNC-Chapel Hill, Children’s Hospital of Philadelphia, and WU) published new findings on the linkages in early brain development to autism:

1) Network inefficiencies in the connections between regions of the brain for high-risk children at 6 months largely predicted severity of autism symptoms, suggesting that early deficits in brain connectivity may contribute to a developmental cascade affecting brain organization and eventually higher-level cognitive processes and social behavior (Lewis et al.).

2) Increased extra-axial cerebrospinal fluid detectable at 6 months could predict diagnosis of autism at 24 months with 69% accuracy (Shen et al.).

3) Brain networks involved in a baby’s learning to walk may help identify whether infants are at risk for autism. A default-mode network, which deactivates in adults when they are performing tasks, is active in babies as they are learning to walk and to control motor functions. Developmental brain regions that comprise this network may be important in autism (Marrus et al.).

NEW RESOURCE INVENTORY FOR IDD RESEARCH AVAILABLE

A recent collaboration of the national network of IDDRCs has resulted in the creation of a new inventory to facilitate awareness about existing databases, subject populations, and biomaterials collections that are known to be available. This inventory might be leveraged to accelerate IDD research. To date, 150 resources have been listed in the inventory.

This inventory may be especially beneficial to junior investigators as a means of jumpstarting new lines of research by harnessing existing resources. The inventory is searchable, and investigators are encouraged to contribute information on shareable data sets.

Information for accessing this resource is available from the IDDRC@WUSTL.
NEW BIOMARKERS FOR POSTHEMORRHAGIC HYDROCEPHALUS IN PRETERM INFANTS

Intraventricular hemorrhage (IVH) is a common, severe neurological complication of prematurity. Up to one-half of preterm infants with IVH develop posthemorrhagic hydrocephalus (PHH). Despite the morbidity associated with PHH and its treatment, there is no consensus about its diagnosis or treatment because of a dearth of quantifiable PHH metrics. For clinical decision making, clinicians rely on imaging-based measurements of ventricular size, which is not specific to PHH.

This study investigated cerebrospinal fluid (CSF) proteins as candidate biomarkers of PHH. CSF was obtained from human infants exclusively via lumbar puncture, which allowed biomarkers to be compared between control and PHH, but also across several other newborn neurological conditions. The entirely novel finding was that CSF levels of APP (amyloid precursor protein), sAPPα (soluble APP fragment), and L1CAM (L1 cell adhesion molecule) are specifically and significantly elevated in untreated PHH.

In addition to their potential role as diagnostic biomarkers, these proteins provide novel insights into the pathophysiology of PHH and possible mechanisms of neural injury and repair.


THE EXOME CLINIC AT WASHINGTON UNIVERSITY

Exome sequencing provides insights into the genetic and phenotypic heterogeneity of Mendelian disorders and highlights the importance of de novo mutations and “blended phenotypes” in rare genetic disorders. This unbiased whole-genome technology has led to shifting of the diagnostic skills of the medical geneticist from focusing on detailed phenotypic characterization to identifying the genetic etiology to “next-generation phenotyping,” which involves interpretation and validation of molecular test results in clinical practice by analyzing observed clinical features. In this study, we present our experience with the “Exome Clinic” with the main purpose of evaluation of the medical geneticist’s role in the optimal interpretation of the exome results and how this might alter the final diagnostic yield.

We found that partnership of the clinician with the molecular laboratory increases diagnostic yield by 7%. An accurate molecular diagnosis allows for precise genetic counseling, has the potential to change clinical management, and is a launching point for personalized medicine.


MODELING AUTISM IN MICE: GENETIC AND ENVIRONMENTAL APPROACHES

New findings from the Dougherty and Gutmann laboratories reveal novel autism-relevant behavioral changes in both genetic and environmental exposure mouse models. Genetically engineered models of Neurofibromatosis type 1 (NF1+/− and NF1GAP CKO) showed changes in pup ultrasonic vocalization, despite meeting other developmental milestones normally.

This communicative behavior was also disrupted in the offspring of mouse dams exposed during pregnancy to fluoxetine, a common selective serotonin reuptake inhibitor (SSRI). A variety of other behaviors were affected in SSRI-exposed mice in adulthood, including alterations in social hierarchy behaviors, perseverative behaviors and tactile hypersensitivity. Re-exposure to fluoxetine in adulthood partially rescued the tactile hypersensitivity while further exacerbating the social phenotype.

Combining maternal SSRI exposure with genetic susceptibility using the Celf6 mutant mice previously developed by the Dougherty lab showed similar behavioral impairments in both the genetic and environmental models, suggesting they act in parallel on the circuits underlying these behaviors, possibly through similar influences on the serotonin system.

Further exploration of this interplay between genetic and environmental factors will be helpful in elucidating the etiology of autism.

Maloney, SE et al. Examining the Reversibility of Long-Term Behavioral Disruptions in Progeny of Maternal SSRI Exposure. ENEURO. 0120-18.2018
Aging with Intellectual and Developmental Disabilities

With the improved treatment and care for individuals with developmental disabilities, individuals with developmental disabilities have seen a dramatic increase in average life expectancy (70 years, compared with 22 years in 1931). Because of these improvements, caregivers and clinicians are faced with new challenges in effectively supporting these individuals throughout the lifespan.

In May 2018, the IDDRC@WUSTL partnered with the St. Louis Association on Aging with Developmental Disabilities (one of the few in the nation) for their 28th annual conference, which was attended by over 300 individuals across 14 states. The conference shared current best practices on a variety of issues in aging with developmental disabilities.

Drs. Joe Piven and Laura Klinger (University of North Carolina at Chapel Hill) presented a keynote lecture highlighting the higher risk among adults with autism for aging-related disorders, cognitive decline, and primary health outcomes. Case studies from Dr. Klinger’s TEACCH Autism Program at UNC helped underscore the need for additional research and training for professional expertise in both aging and autism.

Dr. Christina Lessov-Schlaggar, IDDRC@WUSTL clinical-translational faculty navigator, presented pilot data from a collaboration with the WU Alzheimer Disease Research Center. The project developed and tested a modified version of the Clinical Dementia Rating interview (CDR) developed by Dr. John Morris. The CDR was adapted for assessing dementia in adults with Down syndrome. Additional efforts are in progress to link the instrument into a national consortium on aging in Down syndrome, which would also include imaging and spinal fluid collection to better understand dementia-related biomarkers.

Research Themes of the IDDRC@WUSTL

1. The prediction and prevention of preterm birth
2. Identification of core elements of risk and resilience for IDD
3. Characterization of the developing human brain
4. Understanding cellular and molecular mechanisms of genetic risk for IDD

The mission of the IDDRC@WUSTL is to understand, treat, and prevent disorders of the developing brain through scientific discovery at the levels of cell, circuit, and behavior.

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