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Intellectual and Developmental Disabilities Research Centers: Fifty Years of Scientific Accomplishments

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Abstract

Progress in addressing the origins of intellectual and developmental disabilities accelerated with the establishment 50 years ago of the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health and associated Intellectual and Developmental Disabilities Research Centers. Investigators at these Centers have made seminal contributions to understanding human brain and behavioral development and defining mechanisms and treatments of disorders of the developing brain.

Introduction: History and Overview

In this review, we reflect upon the major transformations that have occurred in the past 50 years in the lives of individuals with intellectual and developmental disabilities (IDDs). We do so primarily through the lens of scientific advances emphasizing contributions of the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers (IDDRCs) on the occasion of their 50th anniversary. During this period, these centers have established a national network of scientists and collaborated with faculty involved in related networks consisting of professional training and clinical centers as well as advocacy organizations. Together, this network has been at the forefront of many critical advances in basic and translational science and in clinical practice involving IDD.

Central to the transformations of the past half century not only has there been a shift toward expanded knowledge of the causes and treatments of neurodevelopmental disorders, but also that individuals with IDD have gone from an often isolated, cloistered existence to one in which community participation and self-determination are both expected and supported. This remarkable shift can be traced to 1961 when President John F. Kennedy called to the attention of the nation the lack of understanding of the etiology, treatment, and prevention of IDDs as well as the availability of community resources and trained professionals for care of those affected. Based on the strategic plan presented in the report by a distinguished committee of experts convened by President Kennedy[1] and through the efforts of the President's sister, Eunice Kennedy Shriver, within 3 years of the President's call to action legislation was passed establishing the National Institute of Child Health and Human Development (NICHD) within the National Institutes of Health (NIH)[2] and proposing the establishment of a network of 12 research centers (now referred to as IDDRCs; see Fig 1 for complete list) to be funded by the newly created NICHD (the NICHD was renamed the Eunice Kennedy Shriver National Institute of Child Health and Human Development in 2008 in her honor).[3] The mandate for these centers was to expand basic and translational research to better understand the causes of IDD and to develop effective therapies. In

addition to IDDRCs, legislation supported the development of university-affiliated clinical and interdisciplinary training programs focusing on individuals with IDD—University Centers for Excellence in Developmental Disabilities (UCEDDs), and Leadership Education in Neurodevelopmental and Related Disabilities (LENDs). Today there are 14 IDDRCs, 67 UCEDDs, and 54 LENDs across the United States, creating a comprehensive professional resource network in the field of IDD.

Establishment of scientific and clinical core facilities through the NICHD program at each IDDRC has been critical to the major research advances described in this review. From the outset, cores provided sophisticated technical expertise and access to equipment for scientists conducting investigations in IDD at all levels of analysis. Examples are numerous and include cores supporting technologies to identify genetic variants associated with IDD through use of targeted next-generation sequencing and whole-exome sequencing. Cores specific to functional genomics are available at most centers to assist in investigations studying global gene expression, noncoding RNAs, and proteomics. As in genetics, the availability of equipment and technical support for multimodal brain imaging (magnetic resonance imaging [MRI], positron emission tomography, electrophysiology) for human and animal studies has been an essential feature of studies of IDD at individual centers and for scientific groups collaborating across centers. Similarly, most centers provide core resources for the study of animal behavior, providing the most advanced and innovative outcome measures in animal models of IDD. Sophisticated behavioral phenotyping for human studies, including standardized neurodevelopmental measures as well as experimental measures such as eye-gaze tracking systems or 3-dimensional surface imaging for dysmorphology assessment, are designed to support clinical trials and longitudinal studies. Additional cores available in most centers have focused on in-depth analysis of IDD in model systems ranging from induced pluripotent stem cell (iPSC)-derived organoids in cell culture to gene- and mutation-specific animal models of IDD. Analyses of such models have been facilitated through availability of sophisticated imaging techniques including optogenetics, high-resolution confocal/multiphoton microscopy, fluorescence resonance energy transfer (FRET), and fluorescence recovery after photobleaching (FRAP), as well as electrophysical assessments in both brain slices and whole organisms.

Plans for the IDDRC network were ambitious from the outset, with available core services designed to serve as a vital infrastructure to facilitate and extend the work of externally funded individual investigators, promote interdisciplinary scientific collaborations among groups of investigators engaged in IDD research, develop new measures and technologies in support of our understanding of gene-brain-behavior relationships, disseminate advances generated by cores, and promote translational science in all its forms. The establishment of IDDRCs within academic centers has also consistently resulted in significant leveraging of institutional support to further facilitate and amplify the resources and capabilities made possible by the IDDRC funding itself. Such leverage in response to the establishment of an IDDRC has contributed to the high level of visibility for IDD research in academic settings and also provided further infrastructure support for training of doctoral and postdoctoral students focusing on IDD. Importantly, this local synergy at individual centers rapidly expanded to include the IDDRC network itself. Here, monthly teleconferences and an annual face-to-face meeting of center directors and invited center personnel (including trainees),

along with NICHD IDD branch leadership help to facilitate and strengthen collaborations and cross-linking of individual programs. Examples include collaboration around genetic variants, standardization of animal behavior studies and iPSC methodologies involving IDD, as well as joint research projects involving clusters of IDDRCs for autism spectrum disorder, fragile X syndrome, and lysosomal disorders and other inborn errors of metabolism.

This work at IDDRCs has often been carried out in conjunction with UCEDDs and LENDs operating in the same institution and with organizations focused on patient advocacy and research, thereby providing a major mechanism for disseminating scientific information generated by IDDRCs. Information from these collaborations has been incorporated into interdisciplinary professional preservice and in-service training programs. Similarly, model clinical services based on scientific advances have been established at university-based clinical centers and widely replicated in community programs. The overall result of these efforts has been substantial progress with respect to diagnosis, health care, and related services as well as developmental benefits for individuals with IDD resulting from both comprehensive and focused behavioral interventions. Increasing numbers of interventions based at IDDRCs are also incorporating drugs targeting molecular mechanisms and evaluating a variety of gene therapies. Through this synergy among our professional networks, IDDRCs have been part of the larger system that has produced major transformations in patient care and significantly improved the quality of life of individuals with neurodevelopmental disorders.

In the following sections of this review, we describe 6 disorders or classes of disorders that are etiologically important in IDD and for which substantial scientific advances have occurred in the context of IDDRCs (except for historical material, all references in this review refer to research conducted within the IDDRC network). For each, we describe dramatic changes in our understanding of the disorders since 1967; the critical contributions of IDDRCs with respect to natural history, pathogenesis, and treatment; the current state of our knowledge; examples of network collaborations; and future challenges and opportunities for the IDDRC programs.

Autism Spectrum Disorder

Over the last 50 years, research from the IDDRCs has dramatically advanced our understanding of the prevalence, comorbidity, and pathogenesis of autism. Although autism is now construed as a family of brain disorders arising from diverse genetic, epigenetic, and environmental causes, persuasive evidence of the strong genetic underpinnings of this condition was not well accepted until the 1977 twin study by Folstein and Rutter.[4] The first convincing conceptualization of autism as a disorder of the brain appeared in a landmark 1979 study by Deykin and MacMahon,[5] documenting the association of autism with epilepsy, ushering in the field of biological and biobehavioral research on autism. The IDDRCs have played a fundamental role in furthering our understanding of autism since these early articles appeared in the literature. Here, we briefly review important contributions from the IDDRCs in the key areas of epidemiology, genetics, neuroscience, and behavior.

Epidemiology and Genetics

A sea change in recognition of the magnitude of the public health impact of autism began in the 1990s and continued through the 2000s through epidemiologic work on the prevalence of autism, including the establishment of a multisite developmental disabilities monitoring network funded by the US Centers for Disease Control and Prevention. This work, with important contributions by IDDRC investigators, demonstrated a 200-fold increase in its prevalence to 1/59, resulting in increasing public awareness and a dramatic increase in research funding.

Investigators at many IDDRCs have had a major role in advances in gene discovery and genetic mechanisms of disease in autism. First reports of syndromic forms of autism and single-gene mutations segregating in families created scientific opportunities to model autism by studying disruptions of single genes. These critical observations led to an appreciation of the etiological heterogeneity of autism with convergence on selected biological systems.[6] In addition, advances by IDDRC scientists in understanding the expression and transmission of inherited liability emerged from family studies.[7]

With the reduction in cost of genotyping from single nucleotide polymorphism arrays to genomic sequencing came an appreciation of the necessity for large-scale collaborations to achieve sample sizes sufficient to detect genetic effects. Leading investigators at many IDDRCs contributed to an unprecedented commitment to resource sharing to rapidly expand genetic samples and biomaterials and analytic pipelines with shared funding by the NIH, Autism Speaks, private donors, and the Simons Foundation. This led to a revolution in understanding the diversity of the molecular genetic landscape for autism and has provided a rich scientific base of dozens of genes with confirmed influence on the development of autism when disrupted.[8,9] Complementing the identification of autism genes was a parallel explosion of studies in model organisms and cells, delineating potential mechanisms[10] and behavioral systems[11] as targets for treatment. Studies of postmortem brains[9,12] and analysis of coexpression networks have converged on disruptions of early synaptic scaffolding, chromatin remodeling, and microglial dysregulation as proximal effects of genetic variants on the development of autism.[13]

Neuroscience and Behavior

Studies of the phenotype have progressed from theoretical conceptualizations about the defining features of the disorder (eg, theory of mind), providing a conceptual framework for the underpinnings of social deficits in autism, to more empirically based measures linked to neurological function and underlying biology (eg, heritable eye-tracking characteristics linked to the development of autism).[14] Parallel efforts have extended to clinical studies of the brain with ever-increasing precision of neuroimaging and electrophysiology to identify aberrant anatomy and function of specific structures (eg, work emanating from IDDRCs laboratories on the role of amygdala and fusiform gyrus in social cognition),[15] linking these findings to specific mechanistic phenomena such as reward circuitry,[16] or specific genetic influences such as CNTNAP2.[17] Critical insights have emerged from the appreciation of autism as a disorder of neurodevelopment with possible immune-mediated intrauterine influences in some cases,[18] and a presymptomatic period in infancy where early deficits in

the development of sensorimotor, visual orienting, and joint attention lead to later manifestations of the defining features of the condition and map on to an unfolding cascade of changes in the development of brain structure and function.[19] Presymptomatic prediction from early brain imaging biomarkers, studies conducted by investigators across 4 IDDRCs as part of the Infant Brain Imaging Study Network, now raise the very real possibility of applying these and other methods prior to onset of the defining symptoms of autism to provide clinically actionable, presymptomatic prediction. In addition, research on molecular neurobiology continues to expand our understanding of the underlying pathogenesis of autism, and holds great promise for the discovery of targeted treatments at the individual level aimed at subsets of emergent social, communicative, sensorimotor, and cognitive competencies that are compromised in specific autistic syndromes.[20]

Rett Syndrome

In 1966, the Austrian pediatrician Andreas Rett published a report on girls who exhibited progressive social and language regression, motor difficulties, and stereotyped hand movements after 1 to 1.5 years of normal development. When the Swedish neurologist Bengt Hagberg and colleagues reported on a series of similar cases in the *Annals of Neurology*, Rett syndrome became recognized by the international medical community.[21] Within a few years it became clear that Rett syndrome is sporadic in over 99% of the cases, affecting approximately 1/10,000 females. Pursuing the genetic cause of Rett syndrome was a challenge given its sporadic nature, but eventually, IDDRC investigators and collaborators discovered that loss-of-function mutations in the *MeCP2* (methyl-CpG binding protein 2) gene cause Rett syndrome.[22] Before long it became evident that mutations in this same gene can also cause autism, bipolar disorder, and juvenile onset schizophrenia.[23] The finding that a sporadic disease like Rett can be genetically determined impacted the fields of autism and other IDDs, whereby the focus shifted to sporadic IDD cases, and IDDRCs across the country reported on many de novo genetic causes of these disorders.

Studies at various IDDRCs have investigated the molecular functions of MeCP2 and its effects on the brain. These studies have revealed that MeCP2 binds to methylated cytosines both in the CG context as well as non-CG context, and that its binding to mCA seems to correlate better with gene expression changes and disease onset. MeCP2 is critical to the function of most neurons and glia; its loss in specific neurons dampens their function and causes subsets of the neuropsychiatric phenotypes, whereas glia contribute to disease progression.[24,25] Beyond cell-specific effects, several studies from IDDRC investigators and others have revealed alterations in synaptic plasticity,[26] circuit activity,[27,28] and circuit maturation.[29] Moreover, IDDRC collaborators showed that deep brain stimulation (DBS) of the fornix in a mouse model of Rett syndrome improved learning and memory, normalized hippocampal plasticity, and enhanced neurogenesis.[30] This has broad implications in that similar DBS might improve learning and memory in a larger population of individuals with IDD irrespective of their genetic basis.

Through the use of genetically engineered mice, we learned that the brain is acutely sensitive to MeCP2 levels, and that both decreases and increases in MeCP2 can lead to neurological and behavioral features that are also observed in humans.[23,31] IDDRCs

investigators recently showed that normalizing MeCP2 levels using antisense oligonucleotides (ASOs) can reverse disease-like features in a mouse model of the human *MECP2* duplication syndrome.[32] The successful use of ASOs for a gene duplication disorder will have impact on many IDDs caused by duplications including Down syndrome (DS). Given that both Rett syndrome and the duplication disorder can be reversed in mouse models,[32,33] there is hope that a treatment can be developed and optimized to help people with these disorders. To date, there are several studies exploring potential therapies including neuroprotective peptides to modulate network activity and restore excitatory/inhibitory balance, as well as gene therapy.[34] The challenges for any intervention will be safety, sustainability of benefits, and reliable measures to assess potential benefits in a clinical setting. IDDRC investigators and colleagues are focused on documenting the natural history of Rett syndrome and MeCP2 disorders, and on understanding its implications for brain function using noninvasive recordings of electrical brain activity.[35] Gathering key clinical information about the rate of disease progression and its course through natural history and brain function studies will guide clinical trials (pharmacological, genetic, or electrophysiological) in the future.

Down Syndrome

DS is a neurodevelopmental disorder first described by John Langston Down in 1866. It was not until the mid-20th century that trisomy 21 was discovered as the underlying genetic cause of DS, which results in the triplication of over 300 genes. Key features of DS include mild to moderate intellectual disability, congenital heart defects, an increased risk for leukemias and other hematologic disorders, and Alzheimer disease (AD) pathology. Through the first half of the 20th century, individuals with DS were generally institutionalized and had very short life expectancies. Since then, improved medical care, access to education, and the provision of comprehensive services and supports has resulted in increased life expectancy and quality of life.

Focusing on recent efforts, IDDRCs have made significant and noteworthy contributions toward the targeted goals of the DS research framework established by the NIH. Mouse models have been developed to identify the cellular and molecular effects of trisomy 21 for studying pathophysiology and disease progression.[36] In addition, induced pluripotent stem cells[37] have enabled the study of molecular and cellular processes that have built upon the seminal research of other IDDRC investigators who identified aberrant neuronal development in DS.[38] Advances in screening, diagnosis, and functional measures have been guided by investigations of life quality in youth,[39] speech and language development,[40] residential transitions,[41] and overall functioning,[42] providing valuable information for establishing outcome measures for clinical trials in DS.[43] Furthermore, investigations in treatment and management for this population have benefitted from careful study of co-occurring conditions such as psychiatric illness[44] and parental well-being.[45]

At present, DS is the most common genetic cause of IDD, with an estimated 300,000 people living with DS in the United States. Prenatal screening through imaging and biochemical marker testing as well as diagnostics using amniocentesis have provided additional information for families to prepare and plan accordingly. Current research on DS continues

to be focused on identification of cellular and molecular mechanisms using preclinical models and to translate findings to clinical trials, including prenatal treatments, to improve cognition.[46]

Moreover, with longer lifespans for people with DS, research in aging and dementia is now an important priority. Natural history investigations of aging in DS at IDDRCs are providing invaluable data on cognition and on fluid-based and neuroimaging biomarkers[47,48] to inform future disease treatment trials in this population. Of note, the DS-Connect registry (https://DSConnect.nih.gov) is now in place to connect families to research opportunities, including clinical trials.[49] One multicenter project studying nearly 500 adults with DS and using DS-Connect to help with recruitment is the Alzheimer's Biomarker Consortium of Down Syndrome, with the goal of identifying the early stages of AD and risk factors for disease progression to inform clinical trials for effective intervention and treatment. Taken together, the research community is now well-positioned to develop clinical trials to improve the quality of life for the growing population of people with Down syndrome.

Fragile X Syndrome and Associated Disorders

Fragile X syndrome (FXS) is the leading inherited cause of intellectual disability. The disorder was first recognized by Martin and Bell in 1943; however, it was not until the 1980s that the genetic nature of the condition and its origin on the X chromosome was confirmed through cytogenetic testing. A major milestone in understanding the disorder occurred in 1991 when an international collaboration, including IDDRC investigators, identified the mutated gene, which was named fragile X mental retardation 1, or *FMR1*.[50] This breakthrough laid the foundation for the development of new diagnostic assays as well as research to understand the effects of the mutation on brain development. The mutation involves expansion of a CGG repeat sequence in the 5′ untranslated region of the gene, which is polymorphic in the general population. Lengths beyond 200 CGGs lead to methylation and loss of expression of the encoded protein, FMRP (fragile X mental retardation protein).[51] FMRP is an RNA-binding protein involved in the regulation of hundreds of mRNAs in postsynaptic neurons, typically through inhibition. Using several animal-model systems, most notably the *Fmr1*-KO mouse, IDDRCs researchers have helped to elucidate the effects of FMRP on brain and behavior.[52,53]

Early work by IDDRC scientists describing the emergence of the behavioral phenotype in humans, documented a declining rate of cognitive development and a variety of comorbid symptoms.[54] Investigators at several IDDRCs have since more fully documented the neuropathology of the syndrome[55] as well as the developmental course of the sensory, motoric, linguistic, social, and psychiatric comorbidities, and clarified those that are unique to FXS.[56] Among the most impairing and well-studied of these comorbid conditions is autism spectrum disorder (ASD), which may occur in as many as 60% of males with FXS and account for 2% to 5% of all ASD cases.[57] Ongoing studies investigating the ASD comorbidity at IDDRCs have the potential to provide insights into the origins of, and treatments for, nonsyndromic ASD as well as FXS. Research at IDDRCs has also focused on understanding the variability in phenotypic expression within FXS, including environmental contributions.[58]

Among IDD conditions, FXS has generated perhaps the most studies of targeted pharmaceutical treatments, with several IDDRCs very active in this regard. Critical to these efforts has been preclinical work using rodent models to understand the mechanism of action of promising compounds. Animal and human studies, many involving IDDRCs, have focused on drugs targeting $GABA_A$ and $GABA_B$ receptors[59] and several other targets. To date, clinical trials for FXS have had only limited success; however, current research in the IDDRC network is focused on developing new outcome measures[60] and clinical trial designs, including combining a parent-implemented behavioral intervention and a selective mGluR antagonist.[61]

Expansions of the *FMR1* CGG repeat in the premutation range of 55 to 200 have been associated with a number of disorder-specific phenotypes, including some not shared with FXS. These premutation disorders include fragile X-associated tremor ataxia syndrome (FXTAS) and primary ovarian insufficiency (POI). FXTAS is a progressive neurodegenerative disorder characterized by intentional tremors, cerebellar ataxia, memory loss, and dementia.[62] This disorder is thought to result from toxicity arising from elevated levels of *FMR1* mRNA carrying expanded CGG repeats. POI is characterized by premature menopause.[63] Ongoing research at several IDDRCs is examining the natural history of these disorders with the goal of identifying risk and protective factors, as not all premutation carriers develop these disorders.

Brain Malformation Disorders

Human brain malformation syndromes present commonly with epilepsy and intellectual disability in childhood, often with comorbid motor and social deficits. In the last half-century, progress in developmental neurobiology has created a foundation for the identification of human brain developmental disorders, including brain malformations. Major advances in neuroimaging and genomics have led to refined characterizations of these disorders, elucidation of their causes, and a deeper understanding not only of disease but also normal human brain development.

The basic neuroanatomical and neurodevelopmental framework for understanding normal and abnormal brain development came from discoveries in many IDDRC laboratories beginning in the late 1960s. Telencephalic development to form the cerebral hemispheres was shown to be initiated through neurogenesis, with proliferation of neuronal precursors in the periventricular germinal matrix, migration of neurons along radial glial fibers to form the layers of the cerebral cortex in an inside-out sequence, and ultimately the structural and functional organization of the cortex.[64-66] Pioneering studies on the intracortical origins of event-related potentials recorded at the scalp also provided the very basis for modern tools for monitoring functional brain activity.[67]

Brain malformations were conceptualized as defects affecting different points along this exquisitely coordinated programmed sequence of events: disorders of progenitor proliferation, neuronal migration, and cortical organization. Neuropathological examination of postmortem human brains and animal models provided an early understanding of how perturbed normal development can lead to neurodevelopmental conditions.[68,69]

Neuroimaging, particularly MRI, revolutionized the field, allowing detailed categorization of disorders in living children according to the nature and distribution of the many types of brain malformations.[70] The early categories of defects of proliferation (eg, microcephaly, macrocephaly), migration (eg, subcortical band heterotopia, periventricular heterotopia), and brain region specification and organization (eg, polymicrogyria) are still used today in classifying brain malformations.[70] Brain malformation syndromes have been identified and refined with increasing phenotypic precision, for example, with lobar specification and association with classic features such as oromotor apraxia with the bilateral perisylvian polymicrogyria pattern. Although initially focused on processes affecting the developing telencephalon, resulting in malformations of cortical development, there is now a growing recognition of disorders of hindbrain development and an expanded role for the cerebellum in normal developmental processes.[20]

Advances in modern genomic science, following completion of the Human Genome Project, have led us from a field dominated by well-defined clinicoradiographic patterns to precise genetic etiologies for a growing number of syndromes and an ever-growing list of genes now implicated in brain development that are ripe for deeper study. A move toward gene-defined syndromes, as applicable, is reflected not only in the modern classification of brain malformations but also by classifications fostered by the NIH through the Clinical Genome resource (ClinGen: https://www.clinicalgenome.org). Some of the earliest gene discoveries related to malformation syndromes resulted from the logical aggregation of patients based on the striking MRI patterns of lissencephaly, subcortical band heterotopia, and periventricular nodular heterotopia.[71,72] In the current era, there continue to be numerous discoveries of single gene defects and copy number abnormalities related to brain malformations, both familial (recessive disorders, X-linked, and dominant) and sporadic, non-inherited, de novo disorders. The recognition of de novo genetic abnormalities has most recently dominated our understanding of brain malformations. In particular, the discovery of postzygotic somatic mutation, leading to mosaicism in conditions such as hemimegalencephaly and focal cortical dysplasia, has led the way for the study of somatic mutation as a potential cause for focal epilepsy more broadly and other neurodevelopmental conditions.[73-75] Studying these disorders at the level of single cells has informed our understanding of the timing and impact of postzygotic events, leading to investigation into the potential role of processes such as somatic mutation (giving rise to copy number variants and single nucleotide variants) and retrotransposition in normal brain development. These discoveries bring an ever-deepening appreciation for the intricacies of processes such as progenitor development and regional specification,[76,77] bringing modern science to classic questions outlined over the decades.

The field of brain malformation disorders, anchored by early discoveries in normal brain development, is now fueled by exciting advances in imaging, genetics, and cellular and animal modeling techniques. In this exciting area, we have the challenge and the opportunity to partner clinical with research efforts and to strive for more precision in our diagnosis, understanding, and ultimately treatment of the consequences of human brain malformations.

Inborn Errors of Metabolism

Following the first identified inborn error of metabolism by Archibald Garrod in 1909, hundreds of these disorders have been discovered, with an overall incidence of about 1 in 1,400 births. What commonly connects these disorders is the deficiency or absence of an enzyme or protein that is necessary for normal metabolism. Inborn errors are most commonly classified into the following categories related to the defective metabolite or organelle involved: amino acid, organic acid, fat, carbohydrate, nucleic acid, lysosome, peroxisome, or mitochondrion. They are varied in presentation and outcome. Some are silent, whereas others present with acute encephalopathy or gradual neurodegeneration. Outcomes can range from typical development to severe IDD and early death and are impacted by early identification and treatment in many cases. The IDDRCs have played a critical role in elucidating a number of these disorders, expanding understanding of their pathogenesis, establishing diagnostic tests, performing natural history studies, and developing innovative treatments. A sampling of these contributions is highlighted below.

Aminoacidopathies

Phenylketonuria (PKU) is the most common aminoacidopathy, with a prevalence of 1 in 14,000. Research led by IDDRC investigators established the efficacy of early treatment with a low phenylalanine diet in preventing severe brain injury.[78] IDDRC investigators also helped establish the newborn screening program for PKU and later identified maternal PKU as a significant cause of IDD in progeny.[79]

Urea Cycle Disorders

Urea cycle disorders consist of 8 enzyme deficiencies that present with episodes of encephalopathy caused by hyperammonemia. Investigators at IDDRCs have determined the enzymatic structure of urea cycle enzymes and identified over 300 mutations in the most common disorder, ornithine transcarbamylase deficiency,[80] markedly improving diagnosis. The outcome of these disorders has been transformed from rapidly fatal to chronic diseases through the development of alternative pathway therapy and liver transplantation,[81] and preclinical gene therapy studies show promise for a future curative approach.[82] Since 2003, IDDRC investigators have collaborated to form the NIH-funded Rare Diseases Clinical Research Center in Urea Cycle Disorders, which has carried out a natural history study as well as clinical trials that have impacted morbidity and mortality in these disorders.[83]

Cerebral Organic Acidemias

Canavan disease (CD) is a progressive neurologic disorder. IDDRC investigators showed CD onset tended to be prenatal followed by a variable clinical course most likely explained by environmental factors and/or modifying genes. IDDRC investigators also showed that CD dramatically impacts all cell types in the central nervous system (CNS).[84]

Lysosomal Diseases

Lysosomal diseases comprise a group of nearly 60 disorders, most affecting the brain and causing severe IDD and related neurological dysfunction. IDDRC research has been pioneering in defining the underlying molecular causes and pathogenesis of many of these

disorders. One example is work demonstrating that Krabbe disease is caused by a defect in the enzyme that degrades the abundant myelin glycolipid galactocerebroside, and that cell death in this disorder is caused by accumulation of a toxin known as psychosine.[85] IDDRC investigators have also been at the forefront of therapy development for lysosomal diseases, including enzyme replacement therapy, bone marrow transplantation, and small molecule/substrate reduction therapy.[86-89]

Peroxisomal Disorders

A variety of peroxisomal disorders involving function and biogenesis are known to cause IDD. IDDRC scientists identified the biochemical defect in adrenoleukodystrophy (ALD) (elevated very long chain fatty acids) and the ALD gene, *ABCD1*. These investigators later developed a newborn screening assay for ALD.[4] Other work has revealed that cerebrohepatorenal syndrome was caused by a defect in peroxisomal biogenesis.[91]

The future of research into treatment of inborn errors of metabolism is likely to reside in gene therapy and gene editing approaches as well as in brain cellular restoration and informed by continued basic and translational research.

The IDDRCs Network and Future Directions

The IDDRCs have been constructed to provide an interdisciplinary perspective involving the disciplines of genetics, neuroscience, and behavioral science to understand better the pathophysiology of disorders causing IDD and to develop innovative therapies. This review has chosen exemplars of the advances made by the IDDRCs since the inception of our network 50 years ago, emphasizing 6 disorders or classes of disorders that have been of central importance to the IDD field and where IDDRCs have played an important role. There are many other examples we could have chosen in other areas that have contributed significantly to the IDD field where IDDRCs have played an essential role. These include research demonstrating the toxic effects of alcohol,[92] fetal surgery to repair neural tube defects,[93] characterization of pediatric acquired immunodeficiency syndrome,[94] and rescue from neonatal brain injury.[95] In addition, groundbreaking randomized clinical trials of behaviorally based interventions have been carried out by IDDRC investigators for groups of young children at risk for IDDs and those with an established neurodevelopmental disorder.[96-100] These investigations produced major scientific advances and have substantially influenced community practices. Ongoing interdisciplinary collaborations that have been a hallmark of IDDRCs continue to create opportunities for a new generation of biobehavioral treatments. For example, clinical trials currently in progress are testing whether drugs that target molecular mechanisms causative of IDD can improve behavioral outcomes.[101]

There are a number of technologies, tools, and interventions that the IDDRCs are likely to use in the next decade to continue progress in the field. Our increasing understanding of epigenetics and microbiome–gene–environment interactions is going to help transform the IDD field. Whole-exome and whole-genome sequencing are rapidly expanding our knowledge of genetic causes of IDD and leading to development of personalized medicine approaches to patient care. Similarly, gene therapy together with gene editing are set to permit curative approaches to certain IDD-causing disorders that are currently untreatable.

Prenatal medicine as a new field holds the potential for enhanced fetal diagnosis and treatment before the clinical manifestations of disease are evident. Artificial intelligence and machine learning will aid in diagnosis, treatment, and (re)habilitation. Moreover, advances in neonatal brain regeneration research as well as organ restoration may benefit many children with disorders causing IDD. What is clear is that the IDDRC network in collaboration with the NICHD and other NIH programs has the potential to continue to lead the way in IDD research.

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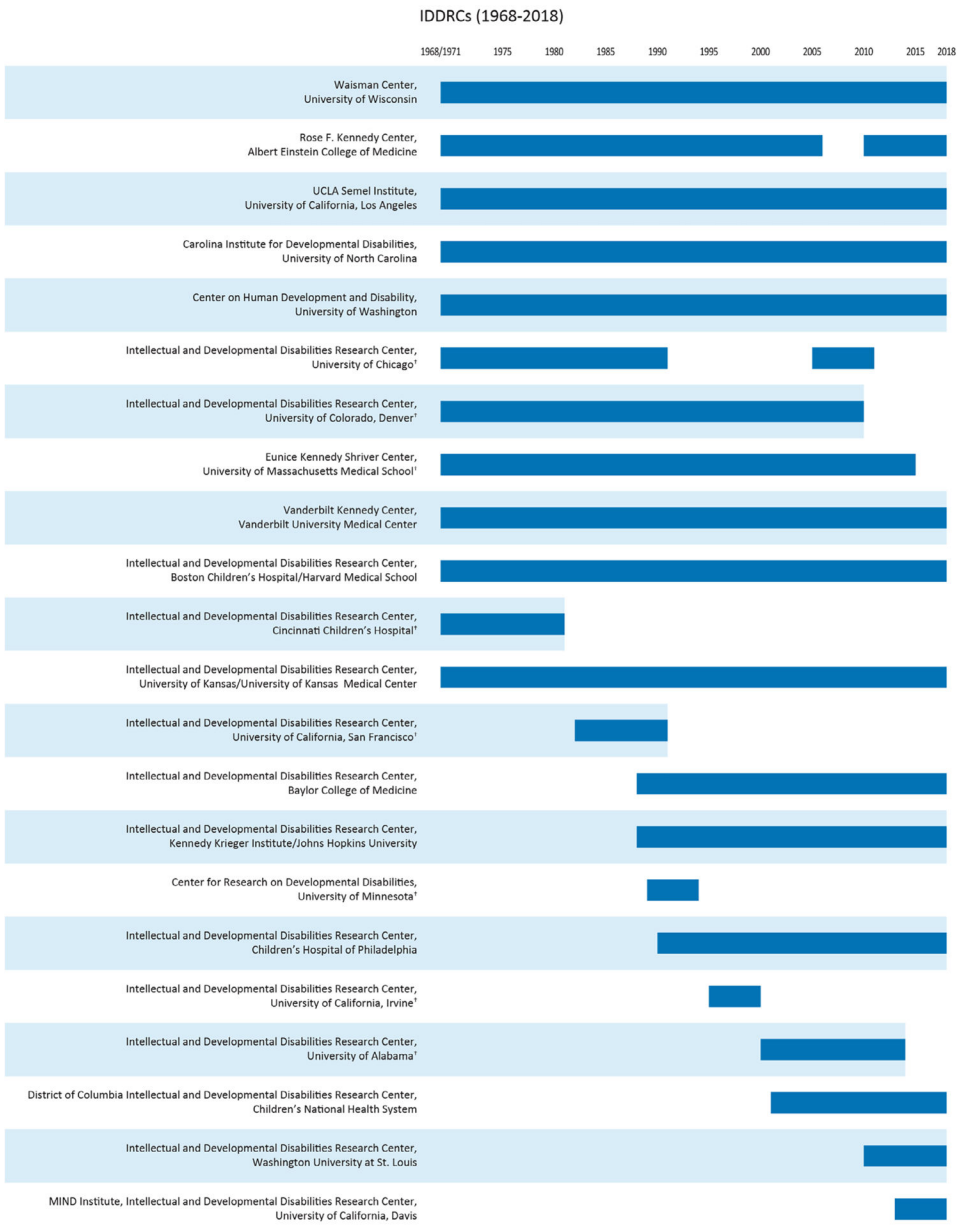

FIGURE:

50 years of scientific accomplishments in the field of neurodevelopmental disorders. Note: Some centers began work earlier than 1968. †Centers no longer funded by the National Institute of Child Health and Human Development. MIND = Memory Impairments and Neurological Disorders; UAB = University of Alabama; UC = University of California; UCI = University of California, Irvine; UCLA = University of California, Los Angeles.