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What Do We Know about Early Onset Neurodevelopmental Disorders?

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Abstract

Early onset neurodevelopmental disorders include a broad range of conditions that affect brain function in children: different diagnostic categories such as fetal alcohol syndrome, attention-deficit/hyperactivity disorder, intellectual disability, and autism spectrum disorders. Combined, they affect more than 10% of all children, and some disabilities are permanent throughout their lifetime. Causes are heterogeneous ranging from social deprivation, genetic and metabolic diseases, immune disorders, infectious diseases, nutritional factors, physical trauma, and toxic and environmental factors. Treatments often involve a combination of professional therapy, pharmaceuticals, as well as home- and school-based programs. This chapter briefly reviews the biological pathways associated with early onset neurodevelopmental disorders and provides useful links to progress in the field. Five main biological pathways are associated with autism spectrum disorders and intellectual disability: chromatin remodeling, cytoskeleton dynamics, mRNA translation, metabolism, and synapse formation/function. Three propositions to foster research, proposed by institutions, researchers, and the community of patients and families, will be discussed: (a) to use more dimensional and quantitative data than diagnostic categories; (b) to increase data sharing and research on genetic and brain diversity in human populations; and (c) to involve patients and relatives as participants in research. Finally, examples are provided of very stimulating initiatives toward a more inclusive world of individuals with neurodevelopmental disorders.

Introduction

Children with neurodevelopmental disorders can experience problems with language and speech, motor skills, behavior, memory, learning, or other neurological functions. These difficulties are also frequently associated with comorbidities such as sensorimotor, sleep, and gastrointestinal problems (Gillberg

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2010). Symptoms of neurodevelopmental disorders often evolve and may improve as a child grows older, but many disabilities are permanent. Diagnosis and treatment of these disorders can be difficult; treatment often involves a combination of professional therapy, pharmaceuticals, and home- and school-based programs. With progress in neurobiology and genetics, the causes of early onset neurodevelopmental disorders are becoming better understood. In this chapter, I summarize current knowledge on the genetic causes and discuss propositions that have been suggested to improve research in this field.

Definition and Prevalence

Early onset neurodevelopmental disorders affect more than 10% of all children (Table 2.1) and often have consequences throughout their lives, in addition to significant effects on their families (Gillberg 2010; Developmental Disabilities Monitoring Network Surveillance Year Principal Investigators 2014; Perou et al. 2013). This grouping is diverse in terms of severity and pathophysiology: fetal alcohol syndrome, attention-deficit/hyperactivity disorder (ADHD), intellectual disability (ID), tic disorder, developmental coordination disorder, dyslexia, specific language disorders, and autism spectrum disorders (ASDs) (Flannick et al. 2014). Neuromuscular disorders, such as Becker or Duchenne muscular dystrophies, could also be included in neurodevelopmental disorders since they also affect cognition in a subset of patients; however, such disorders

Table 2.1 Prevalence and biological pathways associated with early onset neurodevelopmental disorders.

Neurodevelopmental disorders	Prevalence	Proteins or biological pathways
Learning disabilities	2–4%	Chromatin remodeling Metabolism Actin skeleton organization Channels Synaptogenesis Neurotransmission
Dyslexia	5–15%	Neuronal migration?
ADHD	1.7–9%	Synapses? Cortical maturation?
ASDs	0.6–1.2%	Chromatin remodeling Metabolism Actin skeleton organization Channels Synapses
Epilepsy	0.45–1%	Synapses Channels
Fetal alcohol syndrome	0.1–5%	—

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are often considered as a separate cluster because of their predominant symptoms. Boys seem to be at elevated risk compared with girls for most neurodevelopmental disorders, suggesting gender-specific risk and protective factors.

The amount of funding and research dedicated to a disorder is often correlated to its prevalence and severity (Bishop 2010). Thus, it is noteworthy that the amount of research on ID is below the predicted level (Bishop 2010). The causes of early onset neurodevelopmental disorders range from severe social deprivation, genetic risk, metabolic diseases, immune disorders, infectious diseases, nutritional factors, physical trauma, as well as toxic and environmental factors. Among these, knowledge is increasing on genetic risk factors, which, in turn, is motivating new neurobiological research.

The Genetics of Early Onset Developmental Disorders

The list of genes that contribute to early onset developmental disorders numbers in the hundreds. This inherent complexity is exacerbated by the observation that each patient can carry a specific combination of alleles, with large and small effects, that occurs *de novo* or is inherited.

De Novo Mutations

De novo mutations include single base mutations, amplification of trinucleotide repeats, copy number variants (CNVs), large chromosomal rearrangements, and chromosomal aneuploidy (Gilissen et al. 2014). Chromosomal aneuploidy (an abnormal number of chromosomes) is observed in syndromic forms of neurodevelopmental disorders such as Down, Klinefelter, or Turner syndromes. Large chromosomal rearrangements and CNVs can be recurrent in some regions of the genome, such as on chromosome 22q11 (velocardiofacial syndrome), 15q (Angelman and Prader-Willi syndromes), or 17p (Smith-Magenis syndrome). However, in most cases, CNVs which affect from one to hundreds of genes are unique to each patient. A trinucleotide repeat expansion of CGG repeats is observed in fragile X syndrome. This expansion upstream of the *FMR1* gene impedes its expression resulting in increased translation at the synapse. Single nucleotide mutations are another example: X-linked genes, such as *MECP2*, can cause Rett syndrome or autosomal genes, such as *CDH8* or *SHANK3*, can cause ASDs.

Highly penetrant *de novo* mutations probably account for a significant fraction (15–50%) of severe early onset developmental disorders (Hoischen et al. 2014; O'Roak et al. 2011, 2012b; Sanders et al. 2011, 2012; Kong et al. 2012; Iossifov et al. 2012; Neale et al. 2012; Klei et al. 2012). This has been clearly demonstrated for intellectual disability (ID) (Gilissen et al. 2014) and autism spectrum disorders (ASDs) (O'Roak et al. 2012a; Sanders et al. 2011; Neale et al. 2012). Risk factors which increase the occurrence of *de novo* mutations,

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amplifications, deletions, or duplications are better understood (Campbell and Eichler 2013). For example, regions of the human genome flanked by large segmental duplications (such as on chromosome 15, 16p) are more prone to be deleted or duplicated through illegitimate recombination. Increased paternal age has also been shown to be a factor in *de novo* single base pair change. For ASD and ID, *de novo* chromosomal rearrangements and CNVs are more frequently observed in patients compared to controls. In contrast, patients and controls usually carry the same number of *de novo* single base mutations (on average 60–70 *de novo* mutations in each genome of 3 billions of base pairs and 1 in each exome of 60 millions base pair). However, in patients, there is a significant increase compared with controls of damaging (e.g., loss-of-function) mutations in evolutionarily constrained genes expressed in the brain (Figure 2.1) (Neale et al. 2012; O'Roak et al. 2012a; Sanders et al. 2012; Toro et al. 2010).

The vast majority of mutations reported in patients were identified using DNA isolated from their blood (or in some projects from saliva). Thus, *de novo* somatic mutations that occur in specific brain cell lineage were missed (Frank 2014; Poduri et al. 2013). Only studies using deep genomic sequencing and postmortem brain tissues of patients will be able to inform us as to whether somatic mutations in the brain are increased in early onset neurodevelopmental disorders.

Inherited Monogenic and Polygenic Forms

Among patients with early onset developmental disorders, inherited monogenic forms might account for a relatively significant fraction (> 10%) (Zhu et al. 2014). In ASDs, it is estimated that 3–6% of patients are "homozygous knockout" carriers of two loss-of-function mutations in the same gene (Lim et al. 2013; Yu et al. 2013b). In countries with higher consanguinity, the impact of recessive mutations is likely to be higher (Morrow et al. 2008).

Multiple hits in different regions of the genome might also contribute to a susceptibility to early onset neurodevelopmental disorders. Several studies have demonstrated the presence of more than one deleterious mutation in such patients (Girirajan et al. 2010, 2012; Leblond et al. 2012). In a large-scale study of 2,312 children known to carry a CNV associated with ID and congenital abnormalities, 10% carried a second large CNV in addition to the primary genetic lesion (Girirajan et al. 2012). Children who carried two large CNVs of unknown clinical significance were eight times more likely than controls to have developmental delay than controls. Among affected children, inherited CNVs tended to co-occur with a large second-site CNV. No parental bias was observed for the primary *de novo* or inherited site; in the second site, however, 72% of the second-site CNVs were inherited from the mother (Girirajan et al. 2012).

Other studies have supported a multiple-hits model in patients carrying a similar "first hit." In 42 carriers of a 16p11.2 microdeletion, 10 carried an

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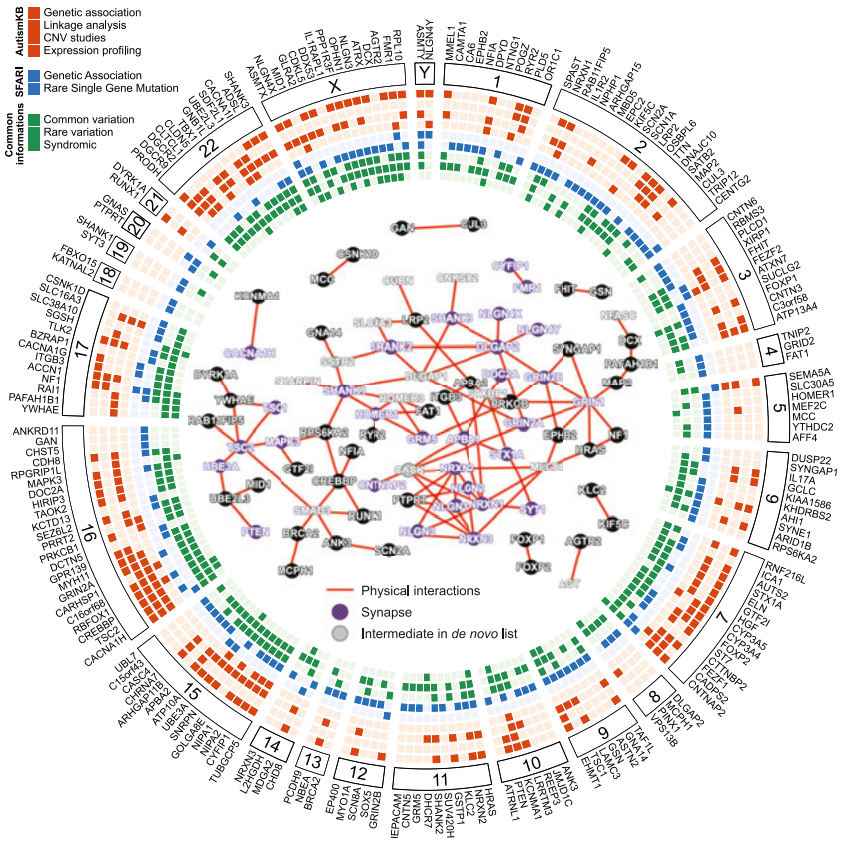

Figure 2.1 Circos plot of *de novo* mutations in autistic spectrum disorder. All coding-sequence variants and copy number variants present in AutismKB and SFARI Gene are shown. A GeneMANIA network analysis (Perou et al. 2013) highlights proteins with synaptic function: 36% of the proteins have at least one interaction with another protein, 61% are expressed in the brain, and 14% are known to be involved in synaptic function. Figure from Huguet et al. (2013), http://gnc.gu.se/digitalAssets/1455/1455513_rev-2cg-bourgerongnc-tb-_4_.pdf (accessed April 7, 2015).

additional large CNV: this is a significantly higher proportion when compared with controls conditional on a large first hit (10 of 42 cases, 21 of 471 controls; P = 0.000057, odds ratio = 6.6) (Girirajan et al. 2010). The clinical features of individuals with two mutations were distinct from and/or more severe than those of individuals carrying only the co-occurring mutation. Another study showed that three patients with ASD carrying a *de novo* SHANK2 deletion were also carriers of a second CNV at the 15q11 locus (Leblond et al. 2012). Two were carrying CNVs, including *CHRNA7* and *ARHGAP11B*; the third was carrying a mutation that removed *CYFIP1*, *NIPA1*, *NIPA2*, and *TUBGCP5*.

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After this initial publication, another child with a neurodevelopmental disorder carrying a *SHANK2* translocation and a *CHRNA7* duplication was reported (Chilian et al. 2013).

In addition to *de novo* and inherited rare mutations, one of the current challenges for geneticists is to identify the myriad of frequent alleles across the genome, which in an additive manner increases the risk of developing a disorder. To date, genome-wide association studies have found few common sequence variants that contribute to risk of early onset neurodevelopmental disorders (Anney et al. 2012). However, quantitative genetics analyses (Yang et al. 2010) estimate that if each common variant has a very low effect, collectively they contribute to a relatively large proportion of the heritability of ASD (15–60%) and ADHD (25–30%) (Klei et al. 2012; Cross-Disorder Group of the Psychiatric Genomics et al. 2013). The same methodology was also used to estimate the contribution of genotyped single nucleotide polymorphisms in the heritability of IQ (> 40%) (Davies et al. 2011; Deary et al. 2012) and on the human brain anatomy (50%) (Toro et al. 2014). Based on these results, even if this genetic information is difficult to translate into clinical diagnostics, the identification of low risk alleles represents an important goal for understanding the genetic architecture of early onset neurodevelopmental disorders (Gratten et al. 2014). Moreover, even weak alleles that have been shown with confidence to influence disease risk are helpful to point to genes and pathways involved in pathogenesis.

Database of Associated Genes

Several genetic databases provide clinical and functional annotation of genes associated with early onset neurodevelopmental disorders. The Online Mendelian Inheritance in Man (OMIM) database[1] catalogues more than 5000 human genetic diseases. Decipher[2] and Database of Genomic Variants[3] are interactive web-based databases which incorporate a suite of tools designed to aid the interpretation of genomic variants. Two databases of genes associated with ASD are updated regularly: AutismKB[4] and SFARI Gene[5] (Huguet et al. 2013). A total of 197 genes are included in both databases, and 481 are additionally included in either one or the other (255 in AutismKB and 226 in SFARI Gene). The main difference between the two databases concerns the selection of the genes. AutismKB usually selects genes from linkage analyses, CNV studies, and genome-wide association studies, whereas SFARI Gene

1 http://www.omim.org (accessed April 7, 2015)

2 http://decipher.sanger.ac.uk (accessed April 7, 2015)

3 http://dgv.tcag.ca/dgv/app/home (accessed April 7, 2015)

4 http://autismkb.cbi.pku.edu.cn (accessed April 7, 2015)

5 https://gene.sfari.org (accessed April 7, 2015)

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usually selects genes from CNV studies, sequencing analyses of large cohorts, and case reports.

Biological Pathways Involved in Early Onset Developmental Disorders

Over the last ten years, tremendous progress has been made in our comprehension of early onset developmental disorders. Animal models (Peca et al. 2011; Bozdagi et al. 2010; Won et al. 2012; Schmeisser et al. 2012; Tabuchi et al. 2007; Jamain et al. 2008; Varoqueaux et al. 2006; Baudouin et al. 2012; Han et al. 2013a; Silverman et al. 2010; Ey et al. 2011) as well as induced pluripotent stem cells (Shcheglovitov et al. 2013; Boissart et al. 2013) have both contributed to better understanding of pathophysiology and new treatment suggestions. Understanding the symptoms and course for each individual as well as the biology (ranging from genetic and environmental risk factors to the neural circuits involved) remains a substantial challenge for geneticists and neurobiologists (Willsey et al. 2013; Parikshak et al. 2013; Gokhale et al. 2012).

Several pathway analyses have been performed using either genetic or transcriptome data to gain insight into the biological functions associated with ASD. Pinto et al. (2010) recently analyzed 2,446 ASD-affected families and confirmed an excess of genic deletions and duplications in affected versus control groups (1.41-fold, $p = 1.0 \times 10^{-5}$) and an increase in affected subjects carrying exonic pathogenic CNVs overlapping known loci associated with dominant or X-linked ASD and ID (odds ratio =12.62, $p = 2.7 \times 10^{-15}$, ~3% of ASD subjects). Consistent with hypothesized sex-specific modulators of risk, females with ASD were more likely to have highly penetrant CNVs ($p = 0.017$) and were also overrepresented among subjects with mutations in genes that encode fragile X syndrome protein targets ($p = 0.02$); this suggests that severe genetic lesions were required to overcome the lower liability to ASDs in girls. Genes affected by *de novo* CNVs and/or loss-of-function single nucleotide variants converged on networks related to neuronal signaling and development, synaptic function, and chromatin regulation. Voineagu et al. (2011) analyzed genes that are differentially expressed between two brain regions (frontal and temporal lobes) in patients with ASD and controls. Interestingly, the typical regional differences between the gene expression profiles of the frontal and temporal lobes were attenuated in patients. A first network module was related to interneurons and to genes involved in synaptic function, and was downregulated in brains from patients compared with those from controls. A second module was enriched for genes related to immunity and microglial activation, and was upregulated in brains from patients with ASD compared with those of controls.

To date, five main pathways have been identified as candidates for early onset neurodevelopmental disorders (Figure 2.2): chromatin remodeling,

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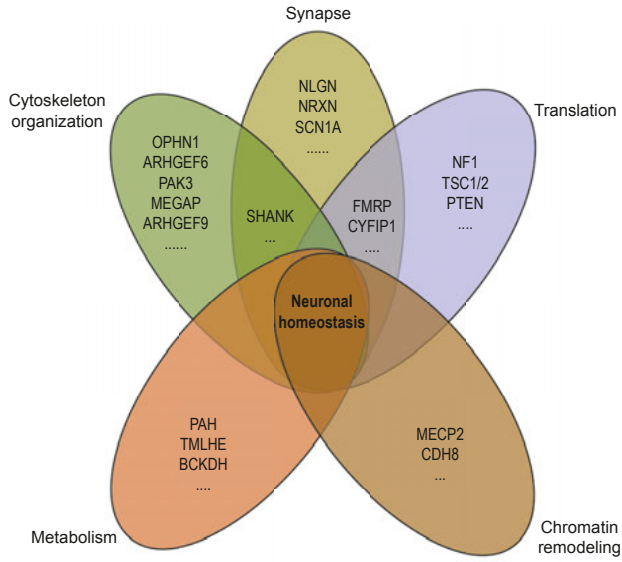

Figure 2.2 Five pathways are associated with early onset neurodevelopmental disorders. For each pathway, mutated genes are indicated.

cytoskeleton dynamics, mRNA translation, metabolism, and synapse formation/function. This list is, however, far from exhaustive.

The first pathway concerns chromatin remodeling and was suggested by reports of mutations in genes such as *MECP2* or *CDH8* in Rett syndrome and ASD, respectively (Amir et al. 1999; Neale et al. 2012; O'Roak et al. 2012a). A second pathway is related to metabolism and includes mutations in genes such as *PAH* in phenylketonuria, *BCKDH* in disorders of branched-chain amino acids, *TMLHE* in carnitine deficiency, or *AGAT* and *GAMT* in creatine-deficiency syndromes. Interestingly, patients with mild forms of inborn errors of metabolism may present with predominantly autistic symptoms (Yu et al. 2013b). Identifying such mutations is of clinical importance since treatments may already be available (Novarino et al. 2012). A third pathway is related to aberrant translation of mRNA-encoding synaptic proteins (Kelleher and Bear 2008) and includes mutations affecting several proteins that normally inhibit translation through the PI3K-mTOR signaling pathway (TSC1, TSC2, NF1, and PTEN) as well as mutations affecting proteins directly involved in inhibiting mRNA translation at the synapse (FMRP, CYFIP1, and EIF4E) (Kelleher and Bear 2008; Costa-Mattioli and Monteggia 2013). A fourth pathway concerns the actin cytoskeleton organization and includes mutations affecting OPHN1, ARHGEF6, PAK3, MEGAP, ARHGEF9, and the regulation of the RhoGTPase, the Ras, the Rab, the Arf, and the JNK pathways (Ba et al. 2013). While mutations affecting these pathways were mostly identified in patients with ID, they might account for a fraction of patients with ASDs (Pinto et al.

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2010). Finally, a fifth pathway is involved in synapse formation and excitation/inhibition balance (Bourgeron 2009; Toro et al. 2010). Several genes associated with ASDs, such as *NLGN3/4X*, *NRXN*, and *SHANK1–3*, appear to be involved in the formation of excitatory and inhibitory synapses (Jamain et al. 2003; Durand et al. 2007; Szatmari et al. 2007). In addition, genes associated with epilepsy, such as *SCN1A*, which encodes a voltage-gated sodium channel, were also found mutated in patients with ASD (O'Roak et al. 2011).

While different, these pathways most likely affect neuronal homeostasis at the end point (Ramocki and Zoghbi 2008; Toro et al. 2010). Some suggest potential drug targets; indeed, some early clinical trials are ongoing to determine whether targeting some such proteins could improve the symptoms of patients (for reviews, see Spooren et al. 2012; Delorme et al. 2013).

Brain Regions and Functions Associated with Early Onset Neurodevelopmental Disorders

In some patients, a problem during cortical brain development can be clearly identified anatomically, such as presence of a double cortex (e.g., mutations in DCX), lissencephaly (e.g., LIS1), microcephaly (e.g., ASPM), or macrocephaly (e.g., PTEN). In other patients, a specific brain region seems to be more affected than others, such as the cerebellum in patients with mutation in the oligophrenin gene (Bergmann et al. 2003). However, the vast majority of neurodevelopmental disorders have less dramatic neuropathology, and thus key brain regions remain largely uncharacterized. In ASDs, the occurrence of a high rate of focal disruption of cortical laminar architecture in the cortex of young children could support dysregulation of layer formation and layer-specific neuronal differentiation at prenatal developmental stages as one mechanism (Stoner et al. 2014). Independently, two studies using ASD gene co-expression networks pointed at mid-fetal cortical glutamatergic neurons as a candidate brain region involved in ASD (Willsey et al. 2013; Parikshak et al. 2013). The interaction between genetics and brain imaging is at a nascent stage and progress in both statistical methods and the collection of large datasets is needed (Medland et al. 2014).

Three Propositions to Improve Research in the Field of Early Onset Developmental Disorders

Although tremendous progress has been made in understanding the causes of early onset neurodevelopmental disorders, several issues offer potential breaks for research in this field. Three propositions are listed below.

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Proposition 1: Fewer Categories, More Dimensions

Recent advances in genomics has demonstrated that an identical genetic variant may increase the risk for a wide range of diagnoses formerly thought of as distinct (Cross-Disorder Group of the Psychiatric Genomics et al. 2013; Moreno-De-Luca et al. 2013; Kim and State 2014). These findings are contributing to an ongoing reconceptualization of current psychiatric nosology. The use of epidemiological samples, studies grouping individuals based first on genetic findings, and efforts to combine existing, categorical schema with dimensional phenotypes and biomarkers all promise important new insights into the etiology and classification of these disorders. DSM-5 now makes it easier to recognize overlap between different diagnostic categories; however, the existing narrow and rigid categories tend to disconnect researchers from the real phenotypes. Recently, initiatives have been undertaken to improve phenotype characterization using more dimensional approaches:

- The Research Domain Criteria (RDoC)[6] was launched by U.S. National Institutes of Medical Health (NIMH) to develop, for research purposes, new ways of classifying psychopathology based on dimensions of observable behavior and neurobiological and genetic measures. This effort is attempting to define basic dimensions of functioning related to known neural circuitry (e.g., fear circuitry or working memory) to be studied across multiple units of analysis, from genes to neural circuits to behaviors, cutting across disorders as traditionally defined. The intent is to translate rapid progress in basic neurobiological and behavioral research into an improved integrative understanding of psychopathology and the development of new and/or optimally matched treatments for mental disorders. A number of articles and editorials have been published describing and commenting on the project. NIMH anticipates that research grants employing this new experimental classification will represent an increasingly large share of its funding portfolio in coming years. NIMH has also announced that clinical trial funding will also be linked to RDoCs.
- The ESSENCE in child psychiatry: Christopher Gillberg (2010) coined the acronym ESSENCE, which stands for early symptomatic syndromes eliciting neurodevelopmental clinical examinations. ESSENCE aims to reflect the reality of children (and their parents) presenting in clinical settings with impairing child symptoms before the ages of 3–5 years, and it cover the areas of general development, communication and language, social interaction, motor coordination, attention, activity, behavior, mood, and/or sleep. Children with major difficulties in one or more (usually several) of these areas are referred

6 For further description and links to articles, see http://www.nimh.nih.gov/research-priorities/rdoc/nimh-research-domain-criteria-rdoc.shtml (accessed April 9, 2015).

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> to health visitors, nurses, social workers, education specialists, pediatricians, general practitioners, speech and language therapists, child neurologists, child psychiatrists, psychologists, neurophysiologists, dentists, clinical geneticists, occupational therapists, and physiotherapists. In reality, however, children are usually seen by only one specialist, when in fact they have needed the input from two or more of these experts. Major problems in at least one ESSENCE domain before the age of 5 years often signals major problems in the same or overlapping domains years later.

In summary, progress in the comprehension of the risk factors for neurodevelopmental disorders will most likely come from dimensional and quantitative data that extends well beyond current psychiatric classification. To enable this, we need to gather information that is currently treated separately by DSM-5 diagnostic categories and located in different laboratories that do not effectively communicate results. Thus, there is a need for increased data sharing (discussed further below).

Proposition 2: More Research on Genetic and Brain Diversity in Human Populations and More Data Sharing

Based on current case-control design, there is a tendency for researchers to know the genotypes and phenotypes of the patients better than those of the controls. Indeed, in the vast majority of genetic studies, controls are often not investigated at the phenotypic level, and in phenotypic studies, controls are very limited in number as well as cultural and social economic status diversity (Manly 2008). As a consequence, early onset developmental disorders are considered binary traits ("affected" versus "non-affected") and this does not take into account the genetic and phenotypic diversity of both "affected" and "non-affected" individuals. The same is true for studies using transgenic mice: most of our knowledge is based on the effect of the mutations in C57BL6 mice. However, we know that mutations might produce a different phenotype in a different strain. The crucial role of the genetic background was very nicely illustrated in a recent paper that showed the phenotypic consequence of the scalloped mutation in different strains of *Drosophila melanogaster* (Chari and Dworkin 2013).

No progress could have been made in the genetics of neurodevelopmental disorders if thousands of genomes had not been sequenced to ascertain their genetic diversity. The same is true for human brains. The first initiatives of the Allen Institute for Brain Science[7] or the Sestan laboratory[8] are impressive in their description of human gene expression at very high resolution. However,

7 http://www.brain-map.org (accessed April 9, 2015)

8 http://medicine.yale.edu/lab/sestan/index.aspx (accessed April 9, 2015)

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if we want to ascertain the links that exist between the variability of genomes and human brains, thousands of brains will need to be studied at the gene expression level as well as functional level, costly and difficult as this may be.

Integrating diversity in our experimental design will require increasing the sample size of our study populations. Indeed, risk factors for early onset neurodevelopmental disorders are either rare with large effect or frequent but with a small effect (McCarroll et al. 2014). In both situations, robust genotype-phenotype relationships are difficult to ascertain in small samples. One opportunity to increase sample size is to foster data sharing. There are many obstacles to efficient data sharing (Poline et al. 2012). There is, for example, an urgent need (a) to agree on an ethically informed consent for research subjects that will allow data sharing, (b) to agree on standardized measures, (c) to change the reward system regarding publications, and (d) to set up a system that will make data sharing both easy and secure.

There is an emerging community of researchers involved in data sharing. In neuroscience, for example, the Neuroscience Information Framework (NIF) and the International Neuroinformatics Coordinating Facility (INCF) have recently been launched. NIF[9] is a dynamic inventory of web-based neuroscience resources: data, materials, and tools accessible via any computer connected to the Internet. Its intent is to advance neuroscience research by enabling discovery and access to public research data and tools worldwide through an open source, networked environment. INCF[10] develops collaborative neuroinformatics infrastructure and promotes the sharing of data and computing resources to the international research community. Neuroinformatics integrates information across all levels and scales of neuroscience to help understand the brain and treat disease. In addition to increasing the sample size of studies, these data sharing initiatives may also lead to a reduction of publication bias in the field of early onset neurodevelopmental disorders (Joober et al. 2012).

Proposition 3: Patients and Relatives as Participants in Research

Many aspects related to the quality of life of patients and their relatives are not adequately addressed by researchers. For example, in ASDs, comorbidities such as gastrointestinal and sensory problems are underexplored.

The movement "no research about me, without me" is a call for patients and their relatives to be more involved in research design. In the United Kingdom, for example, the National Health Service (NHS) initiative INVOLVE[11] is a national advisory group that supports greater public involvement in NHS, public health, and social care research. Other examples include the James Lind Alliance,[12]

9 http://www.neuinfo.org (accessed April 9, 2015)

10 http://www.incf.org (accessed April 9, 2015)

11 http://www.invo.org.uk (accessed April 9, 2015)

12 http://www.lindalliance.org (accessed April 9, 2015)

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the Patient-Centered Outcomes Research Institute,[13] and PatientsLikeMe[14] initiatives for patients that want to monitor their own health and chronic illness. Using such frameworks, patients can propose and conduct their own studies among members, and there is some success to report. For example, a trial of lithium for amyotrophic lateral sclerosis was completed faster than randomized control trials (Wicks et al. 2011). In this study, PatientsLikeMe reached exactly the same conclusion as previous randomized control trials, suggesting that data reported by patients over the Internet may be useful for accelerating clinical discovery and evaluating the effectiveness of drugs already in use. Another example is the initiative for cancer research at Sage Bionetworks. SAGE develops tools so that medical patients can keep their own data rather than storing such data in specified medical institutions. The aim is to offer predictive, personalized, preventive, and participatory (also known as P4) cancer medicine (Hood and Friend 2011). These types of initiatives require the creation of new types of strategic partnerships between patients, large clinical centers, consortia of clinical centers, and patient advocacy groups. For some clinical trials it will be necessary to recruit very large numbers of patients, and one powerful approach to this challenge is to utilize crowd-sourced recruitment of patients by bringing large clinical centers together with patient advocacy groups (Hood and Friend 2011).

Perspectives: Toward a More Inclusive World

For patients, the burden of neurodevelopmental disorders makes daily activities difficult and lowers the odds of living independently. Progress on the causes of neurodevelopmental disorders will hopefully lead to knowledge-based treatments aimed at improving quality of life for those affected. Nevertheless, in addition to improved medical care, innovative initiatives that call for a more inclusive world point toward other important advances. For example, Aspiritech, a nonprofit organization based in Highland Park, Illinois, places people who have autism (mainly Asperger syndrome) in jobs testing software.[15] The Danish company Specialisterne has helped more than 170 individuals with autism obtain jobs since 2004.[16] Its parent company, the Specialist People Foundation, aims to connect one million autistic people with meaningful work.[17] Laurent Mottron, a psychologist working in Montreal, has offered jobs for patients with ASDs in his group, and the perspectives gained have had a positive impact on his research into autism. In his words (Mottron 2011):

[13] http://www.pcori.org (accessed April 9, 2015)

[14] www.patientslikeme.com (accessed April 9, 2015)

[15] http://www.aspiritech.org (accessed April 9, 2015)

[16] http://dk.specialisterne.com (accessed April 9, 2015)

[17] http://www.specialistpeople.com (accessed April 9, 2015)

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"The hallmark of an enlightened society is its inclusion of nondominant behaviors and phenotypes, such as homosexuality, ethnic differences and disabilities. Governments have spent time and money to accommodate people with visual and hearing impairments, helping them to navigate public places and find employment, for instance—we should take the same steps for autistics."

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