Genetic and Epigenetic Networks in Intellectual Disabilities

Hans van Bokhoven

Molecular Neurogenetics Unit, Department of Human Genetics, Nijmegen Center for Molecular Life Sciences, and Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition, and Behavior, Radboud University, Nijmegen Medical Center, 6500 HB Nijmegen, The Netherlands; email: h.vanbokhoven@antrg.umcn.nl

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Abstract

Mutations in more than 450 different genes have been associated with intellectual disability (ID) and related cognitive disorders (CDs), such as autism. It is to be expected that this number will increase three to four-fold in the next years due to the rapid implementation of innovative high-throughput sequencing technology in genetics labs. Numerous functional relationships have been identified between the products of individual ID genes, and common molecular and cellular pathways onto which these networks converge are beginning to emerge. Prominent examples are genes involved in synaptic plasticity, Ras and Rho GTPase signaling, and epigenetic genes that encode modifiers of the chromatin structure. It thus seems that there might be common pathological patterns in ID, despite its bewildering genetic heterogeneity. These common pathways provide attractive opportunities for knowledge-based therapeutic interventions.

INTRODUCTION

CD: cognitive disorder

Intellectual disability (ID): significant limitations both in intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills

Intelligence quotient (IQ): ratio of tested mental age to chronological age, usually expressed as a quotient multiplied by 100

Cognition is used to refer to the mental process of knowing, including aspects such as awareness, perception, reasoning, and judgment. Likewise, the term cognitive disorder (CD) refers to any medical condition that affects how the brain processes and stores information. CDs can be genetic, environmental, or caused by an injury. Intellectual disability (ID), until recently referred to as mental retardation (MR; see sidebar, Rosa's Law), is a prevalent global disease and, together with neuropsychiatric conditions, constitutes the leading source of health care costs in Western society (101, 106, 111). It has been estimated that the lifetime costs for medical care of U.S. children born with an ID in 2000 will be $50 billion (101).

ETIOLOGY OF INTELLECTUAL DISABILITIES

ID is not a single disease entity, but a grouping of a large and heterogeneous collection of syndromic and nonsyndromic disorders that have impaired intellectual abilities as a common hallmark. Clinically, ID is defined by three criteria: (*a*) an intelligence quotient (IQ) below 70; (*b*) limitations in two or more adaptive behaviors, such as communication, self-care, social skills, community use, self-direction, health, and safety; and (*c*) evidence that the mental manifestations began before the age of 18. A further classification of ID is made based on the level of mental impairment: profound ID (IQ<20), severe (IQ 20–34), moderate (IQ 35–49) and mild (IQ 50–69) (8). Often a simpler classification is used in which severe ID comprises all IQ values below 50, and mild ID includes values from 50–70. ID has an estimated prevalence of approximately 2% to 3%, and approximately 0.3% to 0.5% of the population is severely handicapped, indicating that about 85% of all ID patients can be classified as mild ID. Another classical distinction is made between syndromic ID, in which patients have additional anomalies, such as dysmorphic features or metabolic defects, and nonsyndromic ID, in which the intellectual impairment is the sole clinical feature. However, the boundary between the two is often arbitrary because syndromic features may only be recognized when careful comparative clinical examinations are performed in multiple patients with a common etiology. ID can be caused by genetic defects as well as environmental insults that affect the development and functioning of the nervous system, prenatally, perinatally, or postnatally. The most common environmental factors are malnutrition during pregnancy, pre- and postnatal infections, fetal alcohol syndrome, exposure to other neurotoxic compounds, premature birth, and peri- and postnatal asphyxia or other trauma. Such factors have a major contributing role to the prevalence of mild ID (101). By contrast, genetic causes of ID are more frequently observed in the group of severe MR and include chromosome aneusomies, chromosome structural abnormalities, genomic disorders, and monogenic diseases. Such causes account for up to 65% of moderate-to-severe ID, although this percentage varies widely in various studies (25, 26, 101, 108). In accordance with these observations, a conclusive genetic or metabolic diagnosis can be made in approximately 50% to 65% of patients with moderate-to-severe ID, in contrast to 20% for mild ID cases.

ROSA'S LAW

On Tuesday, October 5, 2010, President Barack Obama signed into law S. 2781, "Rosa's Law," which changes references in many Federal statutes that currently refer to "mental retardation" to refer, instead, to "intellectual disability." This change will have a positive effect on the lives of more than six million Americans.

This quote from The President's Committee for People with Intellectual Disabilities, U.S. Department of Health and Human Services announces that the term mental retardation (MR) is outdated and has changed into intellectual disability (ID). It also highlights the enormous impact of this condition on our society because of its high prevalence and because of its lifelong medical implications and social and emotional effects on patients and their families. Despite this, ID still does not receive the public attention and support of research foundations and health care organizations that it deserves.

GENOMIC DISORDERS ASSOCIATED WITH INTELLECTUAL DISABILITY: ZOOMING IN FROM ENTIRE CHROMOSOMES TO SINGLE GENES

With a prevalence of about 1.2 per 1,000 live births, trisomy 21 is the most common classical chromosomal aneuploidy associated with ID. Other common ID-associated chromosomal abnormalities are X-chromosomal aneusomies and a wide variety of cytogenetically balanced and unbalanced translocations. There is also a wide range of recurrent subchromosomal abnormalities that are detectable by conventional karyotyping or by targeted fluorescence in situ hybridization (FISH) analysis on suspicion of a specific syndrome, such as Prader-Willi and Angelman syndromes (15q11.2-q13), Williams-Beuren syndrome (7q11.23), Smith-Magenis syndrome (17p11.2), DiGeorge syndrome (22q11.2), and monosomy of 1p36.1. The detection of chromosomal abnormalities for such clinically recognizable syndromes is currently carried out by the application of specialized polymerase chain reaction (PCR) protocols, such as multiplex ligation-dependent probe amplification and qPCR as a standard procedure in many diagnostic laboratories. Such protocols have also proven to be highly efficient for the detection of subtelomeric deletions, which account for approximately 2.5% of all ID patients (12, 82, 109). It is to be expected that traditional karyotyping and targeted qPCR procedures will soon be superseded by the application of microarray-based technologies for comparative genomic hybridization (array-CGH) (93). Chromosomal microarrays allow the genome-wide identification of submicroscopic chromosomal abnormalities at a very high resolution (several kb), speed, and efficiency. The first array-CGH experiments in patients with ID and dysmorphic features relied on the use of homemade bacterial artificial chromosome (BAC)/P1-derived artificial chromosome (PAC) arrays and had a diagnostic yield of about 10% (135). Currently, a variety of oligonucleotide-based single nucleotide polymorphism (SNP) microarrays are commonly used with increasing genomic coverage of nearly three million probes per array. Several retrospective meta-analysis studies, which together include approximately 40,000 patients with ID, developmental delay, or autism spectrum disorder (ASD), reveal a diagnostic yield of 5% to 20%, depending on the clinical preselection of the patients (62, 93, 114). The wide application of high-density microarrays in research and diagnostic labs has resulted in the identification of a plethora of copy number variations (CNVs) that are associated with ID and in most cases additional congenital anomalies. A number of these CNVs are recurrent interstitial microdeletions and microduplications (136). The clinical features of some of these recurrent CNVs are sometimes consistent enough for the definition of a new ID syndrome; for example, the chromosome 17q21.31 deletion syndrome (75). Most CNVs affect a large number of genes; however, in a few cases a single dosage-sensitive gene could be identified as the cause of the ID phenotype: *RAI1* duplications in Potocki-Lupski syndrome (105), *CHD7* deletions in CHARGE syndrome (137), *MECP2* duplications in MECP2 duplication syndrome (129), and deletions of *EHMT1* in Kleefstra syndrome (74).

SNP: single nucleotide polymorphism

ASD: autism spectrum disorder

CNV: copy number variation

GENETIC CAUSES OF INTELLECTUAL DISABILITY

The elucidation of single gene defects underlying ID has progressed rapidly since the early 1980s. Lesch-Nyhan syndrome and phosphoglycerokinase deficiency were the first human ID disorders for which the genetic basis was resolved. Their elucidation involved functional cloning strategies taking advantage of the metabolic defect associated with these syndromes. However, fragile X syndrome is commonly considered as the first true form of ID that could be explained by a specific genetic defect (133). With a prevalence of approximately 1 in 5,000–6,000 males, the fragile X syndrome is one of the single most

NGS: next generation sequencing

common causes of ID and autism (13, 29, 36). The name fragile X syndrome stems from its co-occurrence with a fragile site, a cytogenetic marker that facilitated the early identification of the genetic defect. The syndrome is caused by expansion of a CGG trinucleotide repeat in the 5′ end of the gene, which leads to transcriptional silencing of the associated *FMR1* gene (28). The breakthrough of resolving the genetic basis of fragile X syndrome was followed by an exponential increase in the number of new genes associated with ID. Initially, mutations were identified in syndromic forms of ID, where multiple patients and families with a consistently recognizable phenotype were available for molecular genetic studies, e.g., Rubinstein-Taybi syndrome (RTS) (102), tuberous sclerosis 1 (131), and alpha-thalassemia/mental retardation syndrome (ATRX) syndrome (54). The identification of genes for nonsyndromic ID was hampered by the fact that each family had to be considered in its own right, as the genetic heterogeneity of the nonspecific ID phenotype precluded the lumping of interfamilial mapping data. Initial successes to elucidate nonsyndromic ID were therefore obtained by positional cloning strategies. For several reasons, X-linked ID (XLID) and nonsyndromic XLID (NS-XLID) were most accessible for molecular genetic studies: (*a*) ID is 30% to 50% more common in males than in females, which is consistent among various populations and suggests a relatively high contribution of X-linked genes to the prevalence of ID; (*b*) physical mapping of X-chromosomal deletions and breakpoints is easier for hemizygous chromosomal aberrations than for heterozygous ones; and (*c*) due to the fact that female carriers of an X-chromosomal mutation are generally able to have offspring, large pedigrees with multiple affected males were available for linkage studies. The successful elucidation of NS-XLID was furthermore accelerated by the establishment of large cohorts of clinically well-characterized XLID families in consortia such as EUROMRX (35) and iGOLD (122). In 1998, the first two NS-XLID genes were identified: *GDI1* (32) and *OPHN1* (18). To date, CNVs and mutations in 41 genes have been connected to NS-XLID (111). Interestingly, *OPHN1* is no longer regarded as an NS-XLID gene because retrospective magnetic resonance imaging consistently revealed cerebellar hypoplasia in patients carrying an *OPHN1* mutation (39). CNVs and mutations in these 41 genes account for approximately 60% of males with apparent XLID, indicating that there is still room for additional genes or mutations that reside in noncoding regions of the X chromosome. Nevertheless, current estimations based on these genes suggest that X-chromosomal defects account for at most 15% of all ID in males, indicating that monogenic X-linked defects cannot explain the excess of ID males.

The elucidation of autosomal genes for nonsyndromic forms of ID has been lagging far behind the successes of NS-XLID. The major reason for this has been the lack of suitable families for accurate mapping of the genetic defect. During the past few years significant progress has been made. One reason for this is the increased application of homozygosity mapping in consanguineous pedigrees with multiple affected individuals. Accurate and rapid identification of shared regions of homozygosity between affected individuals is facilitated by the use of high-density SNP microarrays. Usually, this approach will reveal one or a few regions of shared homozygous haplotypes, ranging in size from a few to several tens of Mb per family. The second innovation that has expedited the successful identification of the causative mutation in autosomal ID is the exponential increase of sequencing capacity accessible to individual labs. Capillary sequencing based on Sanger chemistry is still commonly used, but it is expected that it will soon be replaced by massive parallel sequencing approaches, also known as next generation sequencing (NGS), that can produce hundreds of millions of nucleotide reads in a single experiment. The three most widely used NGS platforms are the Roche® 454 Life Science Genome Sequencer, the Illumina® Genome Analyzer II, and the Applied Bioystems® SOLiD System.

The newest Illumina HiSeq 2000 and Applied Biosystems 5500xl systems have even the capacity to sequence two complete human genomes at 30x coverage in a single run. This enormous sequencing power also allows the detection of autosomal dominant cases of ID (ADID) by screening for de novo mutations in isolated patients. A successful demonstration of this strategy was given by the Canadian Synapse to Disease project (**www.synapse2disease.ca**), in which sequencing of over 400 genes encoding synaptic proteins was carried out in almost 300 patients with ASD or schizophrenia (SCZ), in some cases associated with ID (10). Causative de novo mutations were identified in 14 patients (5% of the total), six with ASD and eight with SCZ. This strategy was taken to a genome-wide level by Vissers et al. (134), who carried out the first whole-exome sequencing in ten isolated patients with unexplained ID and their unaffected parents. This strategy revealed nonsynonymous de novo mutations in six individuals, which were likely to be pathogenic. Recently, exome sequencing revealed a similar high percentage of de novo mutations in ASD patients (99a). Given that ID and ASD occur most often in isolated cases, these findings strongly indicate that de novo point mutations have a strong contribution to the prevalence of these disorders.

INTELLECTUAL DISABILITY, AUTISM, AND A RANGE OF OTHER COGNITIVE DISORDERS SHARE A COMMON MOLECULAR ETIOLOGY

To date, mutations in approximately 450 genes have been implicated in ID (64a; A. Schenck, personal communication), either manifesting as the sole recognizable symptom (nonsyndromic ID; ~50 genes) or in combination with other clinical features (syndromic ID; ~400 genes). For genes of the latter group, ID is sometimes seen in only a subset of all patients with a respective gene mutation. Although the number of ID genes is increasing rapidly, the majority of patients remain without a molecular diagnosis. One reason for this is that routine diagnostic testing is restricted to just a few genes for nonsyndromic or mildly dysmorphic ID phenotypes, i.e., the *FMR1* and *MECP2* genes, or one or a few genes in which the ID phenotype is indicative of a known syndrome. The second reason for the lack of a conclusive molecular diagnosis is that the majority of ID genes have yet to be discovered. It is difficult to predict how many additional ID genes can be expected. Based on the number of approximately 90 known XLID genes (NS and S), a total of 1,500–2,000 genes might be a reasonable estimate.

Mutations in many of the known ID genes give rise to a high degree of clinical variability. For most if not all recognizable ID syndromes, a wide variation is observed in the penetrance of various anomalies that are part of the respective syndrome. Clinical variability can be a reflection of the type of mutation when there is a genotype-phenotype association but can also be seen within families, indicating an influence of other genetic and environmental factors. The clinical variability can be very strong and give rise to different recognizable ID syndromes linked to the same gene, as shown for *ATRX/XNP* (53). Moreover, there are many examples in which clinical variability gives rise to blurring of the boundary between syndromic and nonsyndromic ID, e.g., for *ATRX/XNP* and *MECP2* (47, 73). Finally, there is growing evidence that the mutations and polymorphisms in some genes can be associated with a variety of different CDs. This may not be surprising because of the high comorbidity that is commonly observed between ID and other cognitive impairments, such as autism, attention deficit hyperactivity disorder (ADHD), SCZ, depression, and various behavioral problems. It is estimated that approximately 40% of ID patients have an ASD (89). This number may be an underestimation as a large portion of children who have mild ID are being diagnosed with ASD. This is also the case for Rett syndrome, which is characterized by arrest of early childhood development and profound ID, but which is classified as an ASD. Conversely, ID is seen in 50% to 85% of individuals with autism or ASD (20, 89). The phenotypic overlap between ID and

other cognitive deficits and neurological conditions is mirrored at the genetic level. For a number of genes, mutations have been reported in ID, in ASD, in combinations of the two, and in a variety of other psychiatric conditions, such as ADHD and Tourette syndrome. Examples include *IL1RAPL1*, *SHANK2*, *SHANK3*, *NLGN3*, and *NLGN4* (10, 16, 22, 42, 59, 65, 81, 104), which all code for synaptic proteins (see below). Similarly, mutations and polymorphisms affecting other synaptic proteins have been shown to cause variable neurodevelopmental phenotypes: e.g., *GRIN2B*, *TCF4*, *AUTS2*, *CNTN4*, *CNTNAP2*, and *NRXN1* in ID, SCZ, autism, and other neurological features in various combinations (5, 10, 11, 19, 44, 59, 70, 99a, 118, 119, 147, 148).

Taken together, there is growing evidence to support the notion that ID, autism, and probably a range of CDs share a common molecular etiology at the single-gene level. Thus, CD may constitute a continuum in which strong Mendelian mutations give rise to moderate/severe ID and mild mutations and polymorphisms are associated with mild ID, ASD, and other psychiatric conditions, either as a Mendelian mutation or as a risk factor. Very likely, the concept that various CD have a common molecular basis will be extended upon the identification of genome-wide sequencing efforts in large patient cohorts. Such analyses will also allow the identification of polymorphisms and their cumulative or epistatic interactions in neurological disease. In fact, such interactions are already being revealed, guided by the analysis of genes that have been initially associated with Mendelian ID (19) or in large phenomics studies (113).

MANY INTELLECTUAL DISABILITY GENES CONVERGE ONTO COMMON NETWORKS

It has recently become clear that the bewildering complexity of genes responsible for ID can be understood in terms of modules of several genes acting together in a single pathway or complex, resulting in comparable phenotypes when mutated. Functional correlations have been identified among many of the approximately 450 genes that have been implicated in ID. In some cases, these are restricted to just bilateral protein-protein interactions or regulatory loops, but in several instances more extended functional interaction networks comprising several ID proteins can be recognized. It thus appears that several groups of ID proteins may operate in the same molecular and cellular processes. Obviously, it can be expected that disruption of components of the same molecular network will have a similar phenotypic effect in general (19, 100). Several general molecular and cellular mechanisms underlying the pathophysiology of ID can be recognized, including neurogenesis, neuronal migration, synaptic functions, and transcription and translation (25). Neurogenesis is typically affected in ID disorders comprising primary microcephaly, and these conditions seem to have a common origin in defective centrosome function and DNA repair response pathways (69, 99). Neuronal migration disorders can involve the disruption of various stages of the migration process, including the onset of migration, the actual migration, and the arrest of migration. The arrest of migration is defective in the cobblestone lissencephalies, a specific group of neuronal migration disorders caused by hypoglycosylation of α-dystroglycan, which can be due to recessive mutations in any of six genes with a role in O-glycosylation: *POMT1*, *POMT2*, *POMGNT1*, *LARGE*, *FKTN*, and *FKRP* (130). Defects in neurogenesis, neuronal differentiation, and migration are often associated with ID, as discussed in an excellent review on genes and molecular pathways of the associated disorders (125). Here, I focus on the much larger group of IDs involving shared biological functions in synapse formation and plasticity, cellular signaling, and transcriptional regulation.

SYNAPSE FORMATION, MATURATION, AND PLASTICITY

During development and until adolescence, the brain is prone to extensive structuring of

neuronal connectivity by the formation and elimination of synapses. However, the dynamic regulation of synaptic connectivity is also critical for various aspects of learning, memory, and cognitive functions in the adult brain. The dendrites of most neurons are covered with small protrusions known as dendritic spines, which are the main sites of excitatory synaptic input. Synapses and spines are highly dynamic in their morphology and can undergo rapid structural changes in response to stimuli. This property, called synaptic plasticity, is thought to be the cellular correlate for learning and memory (80, 144). Long-term potentiation (LTP) is a long-lasting enhancement in signal transmission between two neurons that results from stimulation, whereas long-term depression is an activity-dependent reduction in the efficacy of neuronal synapses. These changes in synaptic plasticity can last from hours to days or even years and are associated with alterations in size and morphology of synapses (138). Some of the mechanisms that determine these synaptic changes are beginning to be uncovered and seem to involve the disassembly of adhesion molecules that span the synaptic cleft, the breakdown of actin filaments in the postsynaptic density (PSD), and trafficking of 2-amino-3-hydroxy-5-methyl-4-isoxazole propionic-acid (AMPA) receptors. Functional analysis of the normal and disrupted synaptic functions of ID-associated proteins has contributed significantly to our knowledge of these processes.

Despite the enormous genetic heterogeneity of IDs, changes of dendritic arborization and spine structure are commonly observed in surgical biopsies and postmortem brain tissue of patients with various types of ID without any apparent structural brain anomalies. The first observations were already made 40 years ago in patients with profound ID of unknown etiology (64, 107), and subsequent studies have revealed comparable abnormalities in patients with Down's syndrome, Patau syndrome, fragile X syndrome, and Rett syndrome (46). The dendritic abnormalities are mirrored in mouse models for these disorders (30, 40). It should be noted that the manifestation of dendritic abnormalities is not uniform among the various ID disorders. The number of spines can be either reduced or increased and also spine shape is highly divergent, suggesting that the underlying mechanisms of synaptic distortion can be variable. Indeed, several different mechanisms involving ID genes can contribute to impaired synaptic plasticity and therefore will affect cognitive function. Thus, molecular networks involving ID genes can be found in presynaptic pathways, postsynaptic protein complexes, cytoskeleton dynamics, intracellular signal transduction pathways, transcription regulation, and epigenetic modulation of the chromatin structure (**Figure 1**). A compilation of all genes and associated phenotypes that are discussed in this review is provided in **Supplemental Table 1** (Follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**).

PRESYNAPTIC VESICLE CYCLING

Most synapses in the nervous system are chemical synapses, which respond to stimuli by releasing neurotransmitters. The presynaptic terminal contains a large number of vesicles that are loaded with neurotransmitters; in the case of the excitatory synapse, the neurotransmitter is glutamate. Upon stimulation, the vesicles are translocated to the active zone, docked to the presynaptic membrane and primed. Docking, the initial association of vesicles with the plasma membrane, involves Synaptotagmin, Syntaxin-1 and Munc18-1 (37). De novo mutations in *STXBP1*, encoding Munc18-1, are the cause of Ohtahara syndrome, encompassing infantile epileptic encephalopathy and severe ID (115). In response to Ca^{2+} influx, docked vesicles undergo exocytosis and release neurotransmitters into the synaptic cleft, where these neurotransmitter molecules can bind to their receptors in the postsynaptic membrane. The presynaptic vesicles are covered with Rab proteins, in particular Rab3, which has an important regulatory role in vesicle trafficking. Rab

Dendrite: branched projection of a neuron that is responsible for carrying signals to the cell body of that neuron

Synaptic plasticity: change in the efficacy or connections of the junctions (synapses) between neurons in the nervous system

Long-term potentiation (LTP): long-lasting increase of the response of a postsynaptic neuron to a particular pattern of stimuli from a presynaptic neuron

Long-term depression: activity-dependent reduction in the efficacy of neuronal synapses lasting hours or longer

Postsynaptic density (PSD): electron-dense specialization of the cytoskeleton that was originally identified as a region at the membrane of a postsynaptic neuron, as viewed by electron microscopy

Epigenetic: changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence

Chromatin: the complex combination of DNA and proteins that makes up chromosomes

Supplemental Material

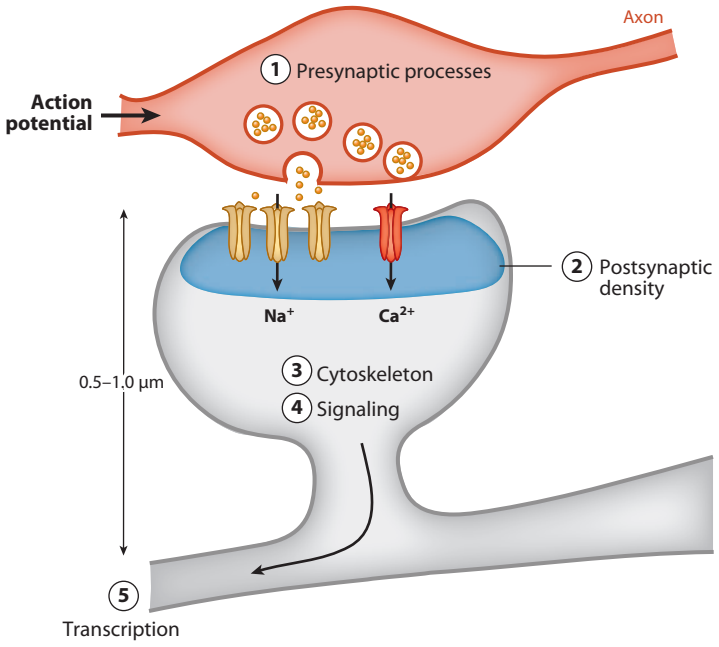

Figure 1

Common neuronal pathways involving intellectual disability (ID) protein. Structure of a typical chemical synapse connecting the axons of a presynaptic neuron to the dendritic spine of the receiving postsynaptic neuron. ① Upon stimulation, neurotransmitter-containing vesicles dock at the cellular membrane, fuse and release their neurotransmitter content into the synaptic cleft. Neurotransmitter receptors at the postsynaptic cell membrane will become activated, which leads to the release of second messengers and into the underlying postsynaptic density (PSD), the opening of ion channels, and generation of a concomitant postsynaptic potential. ② Receptor activation initiates a series of signaling events in the PSD, including receptor shuttling and local protein translation. In addition, other events contributing to synaptic plasticity and formation of (long-term) memory occur: ③ the reorganization of the cytoskeleton, ④ activation of cellular signaling pathways, ⑤ which ultimately affect the control of neuronal gene expression. Each of these processes can be disrupted by gene defects that are seen in patients with ID.

Excitatory synapse: synapse in which an action potential in the presynaptic cell increases the probability of an action potential occurring in the postsynaptic cell

GAP: GTPase-activating protein

GEF: guanine-nucleotide-exchange factor

proteins make up a subgroup of the Ras family of small GTPases, which are typically active in their GTP-bound state and inactive when GDP is bound. The GDP-GTP-bound state is controlled by GTPase-activating proteins (GAPs) and guanine-nucleotide-dissociation-inhibitors (GDIs), which promote the inactive state and guanine-nucleotide-exchange factors (GEFs) to stimulate Rab activity. Two proteins involved in this process have been associated with ID: GDIα and Rab3GAP (**Figure 2**). GDIα is encoded by the X-chromosomal *GDI1* gene, the first gene implicated in nonsyndromic ID (32). GDIα binds and retrieves Rab-GDP to maintain a soluble pool of inactive proteins. Knockout mice have altered synaptic vesicle pools and short-term synaptic plasticity defects (17). However, mutations seem to have little effect on Rab3a, and the cognitive defects might be exerted through other neuronal Rab proteins. Rab39B, a neuronal-specific protein that is localized to the Golgi compartment, has recently been implicated in ID associated with ASD, epileptic seizures, and macrocephaly (52). Its downregulation leads to an alteration in the number and morphology of neurite growth cones and a significant reduction in presynaptic buttons, suggesting that RAB39B is required for synapse formation and maintenance. Rab3GAP is another direct regulator of presynaptic Rab proteins and specifically limits the amount of GTP bound to Rab3A. Mutations in Rab3GAP are found in Warburg-Micro syndrome, a recessive ID syndrome comprising microcephaly, eye anomalies, and hypogenitalism.

Other ID proteins with a direct role in vesicle cycling are IL1RAPL1 and synapsin. The IL1 receptor accessory protein like (IL1RAPL1), involved in nonsyndromic ID (22), ASD, and SCZ (104), inhibits calcium-dependent exocytosis and neurotransmitter release (48). Synapsin I is a neuronal phosphoprotein associated with the membranes of small synaptic vesicles and regulates neurotransmitter release. Synapsin mutations are associated with epilepsy and ID (49). Several other ID-associated proteins are found in the presynaptic compartment and have a role in synapse formation and function, including proteins like FMR1 and OPHN1, which also have important postsynaptic activities. Other ID proteins have an important role in trans-synaptic protein interactions. The *CASK* gene encodes a calcium/calmodulin-dependent serine protein kinase that is a member of the membrane-associated guanylate kinase (MAGUK) family of scaffolding proteins associated with intercellular junctions (9). Calcium/calmodulin-depedent serine protein kinase (CASK) interacts with rabphilin3a, a presynaptic protein involved in synaptic vesicle exocytosis (146).

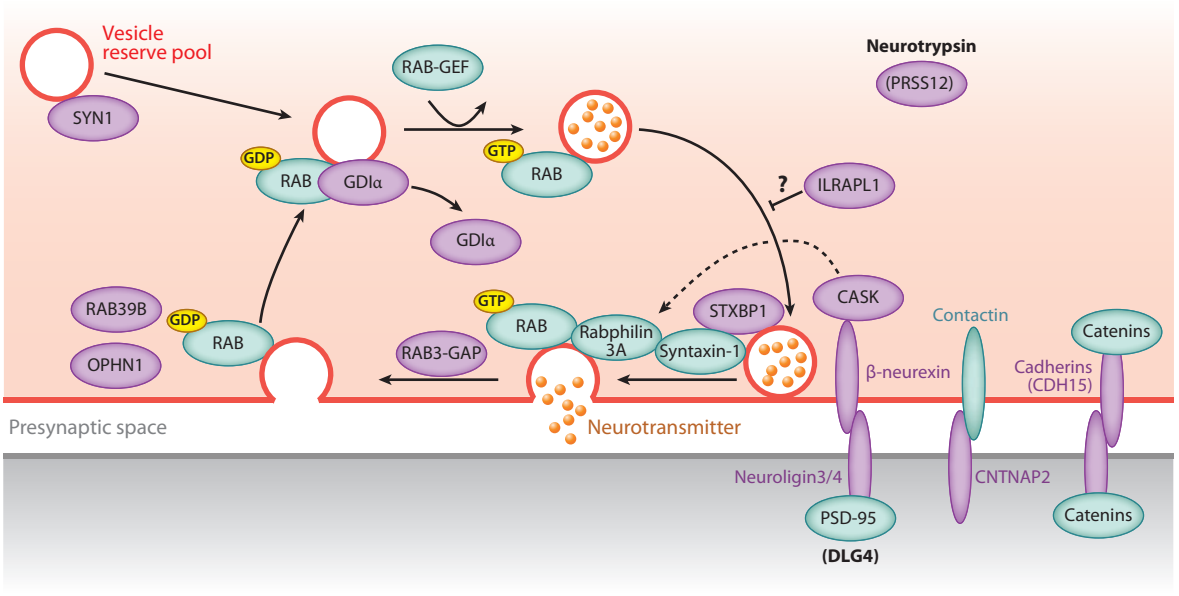

Figure 2

Vesicle shuttling in the presynaptic space. The release of neurotransmitters involves a complex series of steps for packaging of neurotransmitters into vesicles and targeting these vesicles to the cell membrane for releasing their contents. This simplified scheme shows only a limited subset of proteins that are required for this. Many proteins that control these steps are encoded by genes that are mutated in various forms of ID (*purple shading*). Background information about the ID genes corresponding to proteins shown in this figure and the associated phenotypes is provided in **Supplementary Table 1** (Follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**).

Supplemental Material

Moreover, CASK coats the cytoplasmic tails of presynaptic adhesion molecules like synCAM and neurexins (84). Neurexin 1 has been linked to ID and to a range of other neurological conditions. The same is true for its binding partners, neurligins 3 and 4 and the synaptic cell adhesion protein CNTNAP2. Interestingly, mutations in *CNTNAP2* and *NRXN1* lead to comparable ID phenotypes resembling the Pitt-Hopkins syndrome, and both determine the level of the presynaptic protein bruchpilot, a protein that is critical for active zone structure and neurotransmitter release (147).

ORGANIZATION OF THE POSTSYNAPTIC DENSITY

There is increasing evidence that disruption of signaling pathways both in excitatory glutamatergic neurons and in inhibitory GABAergic neurons contribute to the cognitive impairment and behavioral anomalies in ID and ASD (24, 88). However, physiological studies toward the synaptic role of ID-associated proteins were initially focused on excitatory glutamergic neurons of the hippocampus, which are an integral part of memory formation. Consequently, most knowledge has been collected for postsynaptic processes in excitatory neurons, on which this review will be concentrated. Two main types of glutamate receptors are found in the postsynaptic dendritic spines of excitatory glutamate synapses, the N-methyl-D aspartate (NMDA) and the AMPA receptor. Synaptic strength is determined by the number of AMPA receptors that are exposed to the synaptic cleft. Mutations in genes encoding subunits of AMPA and NMDA receptors have been linked to variable neurodevelopmental phenotypes. Mutations in the X-linked *GRIA3* gene, encoding a subunit ionotropic AMPA receptor are associated with moderate cognitive impairment in humans

(142). In addition, translocations and de novo mutations affecting either *GRIN2A* or *GRIN2B*, encoding the NMDA receptor subunits NR2B and NR2A, are associated with ID and/or epilepsy (44). Along with such mutations that directly affect ionotropic glutamate receptors, evidence is culminating that mutations in other ID genes affect trafficking and stabilization of these receptors. For example, OPHN1 controls synapse maturation and plasticity by stabilizing AMPA receptors (96).

Neurotransmitter receptors and other synaptic membrane proteins are anchored to the underlying PSD, an electron-dense protein network that is connected to the actin cytoskeleton. Almost 1,500 proteins have been assigned to the PSD proteome, of which 133 have been associated with primary nervous system disorders (14). This is significantly more than expected by random chance, suggesting that the disruption of many more PSD proteins will underlie neurological disorders of currently unknown etiology. Indeed, recent high-throughput sequencing of ID patients has revealed mutations in additional PSD genes (V. Kalscheuer, personal communication). MAGUK proteins and other PDZ-domain proteins have a major role in scaffolding of the PSD and in trafficking of ion channels and neurotransmitter receptors. Protein networks involving these PDZ proteins are affected in various forms of ID and autism (**Figure 2**). SAP97 (*DLG1*), which itself has not been implicated in ID, regulates AMPA receptor dynamics and associates with CASK to mediate sorting of highly mobile vesicles containing NMDA receptor subunits NR1 and NR2B via a new secretory mechanism that bypasses the Golgi network (67). Furthermore, the MAGUK proteins SAP102 (*DLG3*; XLID) and PSD95 (*DLG4*) also associate with NMDA receptors and other major PSD proteins, such as HOMER, calmodulin-dependent protein kinase II (CaMKII), the synaptic Ras-GAP SynGAP, DLG-associated protein DLGAP/GKAP, and several SH3 and multiple ankyrin repeat domain proteins (SHANKs). HOMER and SHANK, which are among the most abundant scaffolding proteins in the PSD, form a polymeric network structure serving as an assembly platform for other PSD proteins (61). SynGAP, a prominent Ras-GAP in the PSD, appears to be an important regulatory switch, as it regulates many synaptic processes (112). Along with the timing of spine formation and AMPA receptor trafficking, it plays a critical role in NMDA receptor–mediated Ras signaling (via CaMKII), and it regulates steady-state and activity-dependent phosphorylation of the cytoskeleton protein cofilin (21).

Animal model studies and naturally occurring human mutations highlight the importance of PSD protein complexes in learning and memory and other cognitive processes. A remarkably high number of de novo mutations and genomic aberrations have been identified in *SHANK3*, *SHANK2*, *SynGAP1*, and *GKAP* in patients with ID, ASD, and SCZ (10, 16, 42, 103). Thus, *SynGAP1* mutations may account for 3% to 5% of isolated nonsyndromic ID (58, 60) and de novo *SHANK3* mutations for up to 1% of ASD (94) and 0.5% of SCZ patients (50), in both cases with or without associated ID (10).

REGULATION OF POSTSYNAPTIC PROTEIN LEVELS

Local regulation of protein levels in the PSD is an important mechanism in the control of synaptic plasticity. The fragile X protein FMRP (fragile X mental retardation protein) is an RNA-binding protein that associates with microRNAs and Dicer to regulate the local translation of associated mRNAs (68). Several groups have recently shown that the FMRP protein is a regulator of the local synthesis of synaptic proteins, including PSD-95, CaMKIIα, GluR1/2, and Arc, which may contribute to the ID and autistic features of the fragile X syndrome (95, 145). Another level of regulation of PSD proteins is through ubiquitin-mediated protein turnover. For example, mGluR stimulation exerts bidirectional control over FMRP level by activating

translation and ubiquitin-proteasome system (UPS)-dependent proteolysis for the up- and downregulation of the protein, respectively (63). A growing group of ID proteins are directly involved in UPS-mediated protein degradation, including UBE3A (Angelman syndrome), UBE2A, HUWE1, CUL4B (all XL-ID), and UBR1 (Johansen-Blizzard syndrome). The importance of UPS-dependent degradation for synaptic plasticity was recently shown for UBE3A (55). Ube3A transcription in mice is induced by experience-driven neuronal activity, which in turn promotes the degradation of Arc, a synaptic protein that regulates the internalization of AMPA receptors. Disruption of Ube3A function in neurons led to an increase in Arc expression and a concomitant decrease in the number of AMPA receptors at excitatory synapses. Thus, it seems that the tight regulation of postsynaptic protein levels is critical for normal learning and memory processes.

CYTOSKELETON DYNAMICS IN DENDRITIC SPINE DEVELOPMENT AND MORPHOLOGY

Dendritic spine morphology is highly plastic and changes of shape or size of spines can occur within seconds. The dynamic morphology of spines is the consequence of continuous polymerization and breakdown of actin filaments and dynamic microtubules in the spine (66, 98). Members of the family of RhoGTPases, such as Cdc42, RhoA, and Rac, are key regulators of the actin and microtubule cytoskeletons. Several regulators and effectors of these RhoGTPases in cytoskeleton remodeling are associated with ID (98). These proteins include regulators of the GTP/GDP-bound state of RhoGTPases: the RhoGAPs oligophrenin (OPHN1; ID with cerebellar hypoplasia), MEGAP ($3p^-$ syndrome), and OCRL1 (Lowe syndrome), and the RhoGEFs ARHGEF6/αPIX (nonsyndromic ID), ARHGEF9/collybistin (hyperekplexia, epilepsy, ID), and FGD1 (syndromic ID). The ID phenotypes associated with mutations in these genes are highly variable, which is in line with the notion that the encoded proteins regulate different RhoGTPases in different signaling pathways (97). PAK3, which is involved in nonsyndromic ID (4), is an effector of Rac and Cdc42. PAK proteins together with the Rho kinase ROCK activate LIMK1, which in turn phosphorylates cofilin, thereby inhibiting its actin-depolymerizing activity (7). The *LIMK1* gene is located in the minimal deletion of Williams-Beuren syndrome and is considered to be causative for the remarkable neurological features of the syndrome, characterized by moderate-to-severe ID with relatively good verbal performance and a friendly character (cocktail party personality). Indeed, *Limk1* knockout mice display striking abnormalities in spine morphology and synaptic function, and show altered fear responses and spatial learning abilities (91). Another interesting pathway downstream of Rac1 is channeled through the cytoplasmic FMRP-interacting protein 1 (CYFIP1), which links Rho GTPase signaling to the FMR1 protein disrupted in fragile X syndrome. It was shown recently that protein complexes containing CYFIP1 also coordinate Arf1 and Rac1 signaling during the biogenesis of clathrin-coated adaptor protein 1 (AP-1)-coated transport carriers that connect the *trans*-Golgi network and the endocytotic pathway, a process that is highly dependent on actin dynamics (6). Interestingly, Arf1, another small GTPase of the Ras superfamily, is regulated by the ArfGEF IQSEC2, which was found to be mutated in several families with nonsyndromic XLID (117). In addition, mutations in the *AP1S2* gene encoding the sigma 2 subunit of the AP-1 complex are seen in several families with XLID, hydrocephaly, and calcification of basal ganglia (123).

CELLULAR SIGNALING CASCADES

Activation of glutamate receptors initiates a number of postsynaptic cellular signaling cascades, including the Ras signaling pathway. The Ras pathway is disrupted in a growing

group of neuro-cardio-facio-cutaneous conditions (NCFCs): Noonan syndrome and Noonan-like syndrome, Costello syndrome, neurofibromatosis, LEOPARD syndrome, CFC syndrome, and Legius syndrome (140). The phenotype network comprising these NCFCs is mirrored by a gene network consisting of genes encoding the Ras GTPases HRas and KRas, downstream effectors of Ras (RAF1, BRAF, MEK1, MEK2, and RSK2) and regulators of the Ras-MAPK pathway (SHP2, SOS, NF1, SPRED1, SHOC). The degree of ID is highly variable in the NCFCs and in some cases specific for certain tasks. Interestingly, there is a high degree of both allelic and locus heterogeneity for these conditions. Most of the clinically discernable NCFCs can be caused by mutations in several Ras-MAPK pathway genes, and conversely, each of those genes can be causative for a number of individual NCFCs. As a result, the NCFC-Ras pathway is one of the most instructive examples of genotype-phenotype associations at the level of networks. Very likely, extension of these networks can be expected both in the phenotype space as well as in the genotype space. Indeed, mapping of a chromosomal breakpoint in a patient with a Noonan syndrome–like phenotype revealed a causative disruption of the *MYST4* gene, which encodes a histone acetyltransferase (C. Thiel & A. Rauch, personal communication). Although a direct link between MYST4 and the Ras-MAPK pathway is not immediately evident, it was shown that the disruption of *MYST4* in patient cells and in cells from the *Myst4* mouse model *Querkopf* gives rise to reduced acetylation of histone 3 and reduced expression of genes, with a clear enrichment of genes from the Ras-MAPK pathway, such as *Mek1/2* and *Erk1/2*.

The PI3K-mTOR pathway is emerging as another major signaling cascade that is commonly disrupted in a variety of neurological disorders constitute ID and ASD. PI3K-mTOR signaling controls translation, which is prerequisite for memory consolidation (33). Disruption of translational control through the PI3K-mTOR pathway has been reported for a variety of ID and ASD syndromes (77), including fragile X syndrome (15), tuberous sclerosis (43), Cowden disease (85), and Rett syndrome (110) (**Figure 3**).

EPIGENETIC REGULATION OF TRANSCRIPTION

The generation of long-term memory critically relies on transcription and translation. Inhibitors of translation and transcription affect long-lasting synaptic plasticity and memory (33). The classical studies of Kandel and colleagues in *Aplysia* have demonstrated that the transcription factor cAMP response element-binding protein (CREB) is a critical mediator of long-term memory formation by activating genes such as the immediate early gene *c-fos* and the brain-derived neurotrophic factor (*BDNF*). CREB is constitutively expressed in many cell types and can be activated by phosphorylation through a variety of signaling pathways. In neurons, these include the increase of intracellular Ca levels upon stimulation of NMDA receptors, the increase of the second messenger cAMP following activation of G protein–coupled receptors, and activation of the Ras-MAPK pathway. Besides CREB, a plethora of other transcription factors (TFs) and transcription regulators have been implicated in synaptic plasticity and memory formation (3). Moreover, a growing number of ID genes encode proteins that have a direct or indirect role in transcription, such as TF, TF complex–associated proteins, and proteins that regulate transcription by modulating the chromatin structure. The modulation of the chromatin structure, popularly referred to as epigenetic regulation, are the covalent modifications of genomic DNA by DNA methylation and posttranslation modification of the associated histone proteins by acetylation, methylation, phosphorylation, and more rarely ubiquitination, sumolyation, and ADP-ribosylation (**Figure 3**). The palette of various repressive and permissive chromatin modifications determines the accessibility of the associated DNA for the transcription machinery, and

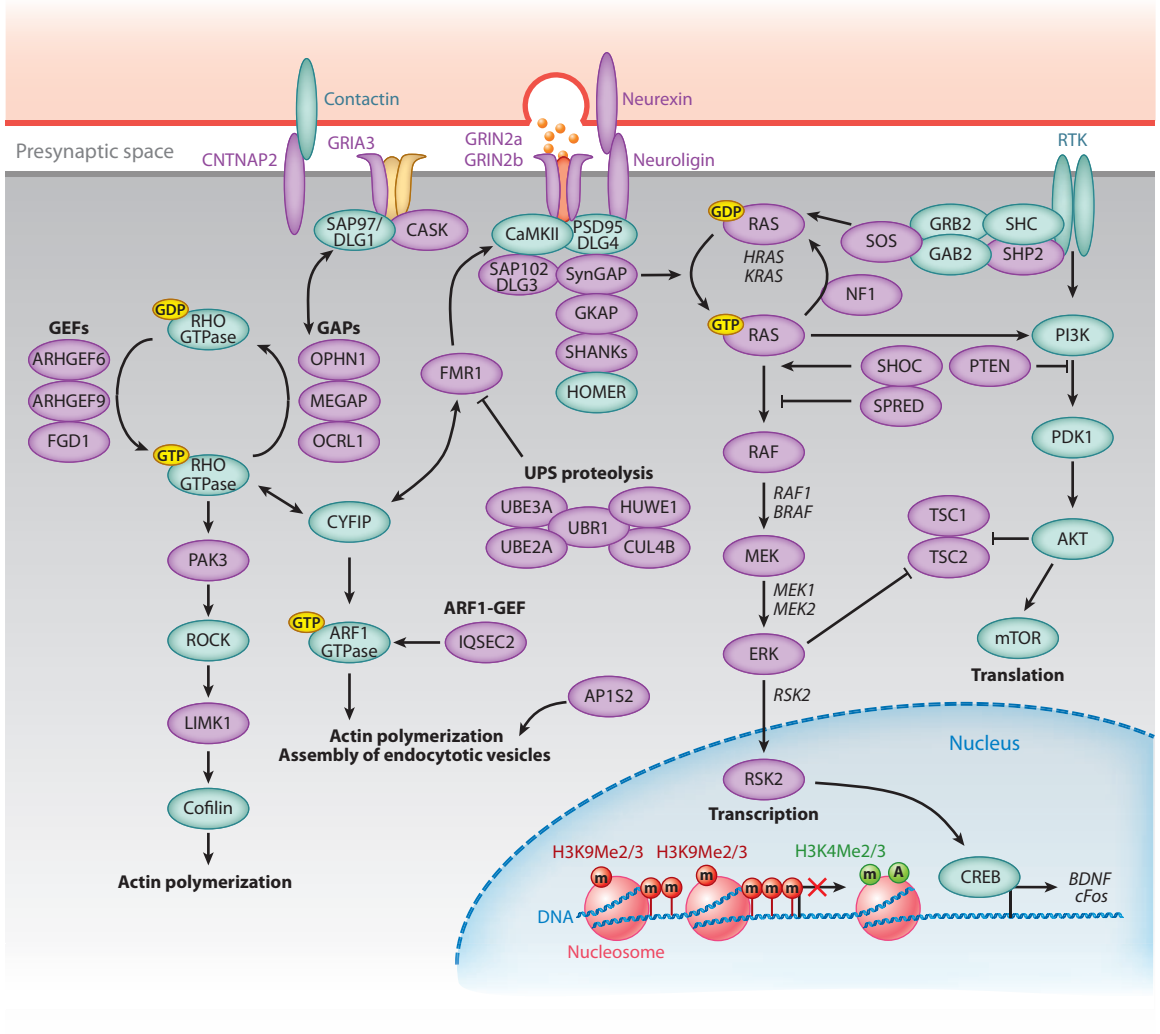

Figure 3

Postsynaptic protein networks and pathways involving intellectual disability (ID) proteins. This schematic drawing shows the most important postsynaptic pathways: the organization of the postsynaptic density, cytoskeleton dynamics, cellular signaling cascades, and epigenetic regulation of transcription. Purple proteins have been implicated in ID. The DNA in the nucleus is wrapped around nucleosomes consisting of histone proteins. Some histone and DNA modifications are indicated: the repressive ones indicated in red [DNA methylation (m) and methylation of H3K9me2/3] and activating ones in green [H3K4me2/3 and histone acetylation (A)].

thus dictates where and when genes are expressed. Epigenetic regulation has captured a lot of attention lately because it constitutes a mechanism that has many features that are suitable for the formation and consolidation of long-term memory (34). First, epigenetic modifications are sufficiently dynamic and can be induced in nondividing cells by neuronal stimulation. Second, epigenetic modifications can be perpetuated through neural connectivity. Third, epigenetic modifications are not only dynamic, but can also be relatively stable and exert their effect on transcription for a long time. Indeed, there is a large body of evidence

Supplemental Material

that the regulation of the chromatin structure is required for induction of synaptic plasticity and memory formation in the hippocampus and prefrontal cortex. In particular, acetylation and phosphorylation have been established as critical early events in establishing hippocampal memory (2, 27, 56, 83, 120). Interestingly, these modifications are mediated through activation of the ERK/RSK signaling pathway. In addition to histone acetylation and phosphorylation, DNA methylation and histone methylation have recently been established as dynamic regulatory mechanisms to facilitate memory formation. Memory consolidation in contextual fear conditioning paradigms was associated with increased DNA methylation and histone 3 lysine 4 trimethylation at the *Bdnf* gene promoter, resulting in altered *Bdnf* expression in mouse hippocampus (57, 87, 92).

Several of the epigenetic modifications that are required for memory formation are affected by gene mutations that have been identified in ID. Approximately 10 ID genes encode proteins that have a direct role in chromatin modification, the epigenetic writers (**Supplemental Table 1**) (79, 126). The CREB binding proteins CBP and p300, which are both mutated in RTS, are histone acetyltransferases that interact with CREB to regulate expression of neuronal target genes. Reduced CBP-mediated acetylation in a mouse model for RTS is associated with reduced hippocampal LTP (2). DNMT3B, which is mutated in immunodeficiency-centromeric-instability-facial anomalies (ICF) syndrome 1, and its paralog DNMT3A are involved in the de novo DNA methylation. Ablation of DNA methyltransferase activity in mice inhibits hippocampal LTP. Moreover, simultaneous conditional knockout of Dnmt1 and Dnmt3a in adult neurons of the mouse forebrain affects spatial memory in the Morris water maze test and memory consolidation, but not acquisition, in a contextual fear conditioning assay (45, 141). Finally, euchromatic histone methyltransferase (EHMT), which is mutated in Kleefstra syndrome, appears to be a key regulator of memory consolidation (78, 116). Mutation of this gene in *Drosophila* gives rise to reduced dendrite branching. In addition, the mutant flies showed normal learning, but short-term (30 minutes) and long-term (24 h) memory was severely impaired in a courtship conditioning paradigm. Interestingly, these memory deficits were associated with reduced histone methylation at the 3′ end of genes, with a striking and significant enrichment for genes with a known role in learning and memory (78).

Another group of approximately 20 genes encodes proteins that have been found in epigenetic protein complexes and that act as coregulators of transcription, the readers and maintainers of the epigenetic code (**Supplemental Table 1**) (79, 126). Many functional interactions have been established between the proteins of both groups. The methyl-CpG-binding protein MECP2 involved in Rett syndrome and other forms of ID and ASD has been identified in many such complexes, both at repressive and permissive chromatin. Thus, MECP2 has been found in transcriptional complexes with several other ID proteins, including ATRX/XNP, DNMT3b, CBP, RSK, and CDKL5 (reviewed in 79). Cooperative and antagonistic interactions between epigenetic ID genes have been shown to regulate the transcription of genes that have been linked to learning and memory. Transcriptional repressor complexes containing REST (repressor element 1 silencing transcription factor)/NRSF (neuron-restrictive silencer factor) appear to have a prominent role in this (57, 86, 126). Other than MECP2, ID proteins associated with the REST complex are EHMT1, JARID1c, MED12, CDK8/CDC2L6, DYRK1a, and KRAB-domain Zinc finger genes (**Figure 3**, **Supplemental Table 1**). The histone methyltransferases (H3K9me2/3) EHMT1/GLP and EHMT2/G9a and the histone demethylase (H3K4me2/3) JARID1c/KDM5c both induce repressive chromatin marks and cooperatively repress gene expression (1, 71, 121). H3K4me2/3 is a mark for active transcription, which is transiently upregulated at neuronal target genes upon memory formation (57). This transient increase in H3K4 trimethylation

at specific neuronal promoters coincides with altered DNA methylation and altered MECP2 binding. Histone deacetylases contribute to transcriptional silencing activity by removing acetyl groups from histone tails. HDAC4 has recently been linked to syndromic ID; however, a specific link between HDAC4 and components of the REST complex has not yet been established (139). DYRK1a is also linked to REST. The *DYRK1a* gene is contained in the Down syndrome critical region, and its duplication may contribute to the cognitive deficits in Down syndrome. Moreover, an intragenic *DYRK1a* microdeletion was recently identified in a patient with ID and microcephaly (127). Finally, the TCF4 protein, implicated in Pitt-Hopkins syndrome and affective bipolar disorder, associates with SMARCA- and REST-containing epigenetic complexes (38). Epigenetic silencing by the REST complex occurs through interaction between EHMT proteins and the MED12 protein, which is contained in the core module of the mediator complex (41). The mediator complex is a large complex consisting of at least 20 different subunits that links regulatory complexes to the RNA polymerase II transcriptional machinery (23). *MED12* mutations have been identified in FG syndrome and Lujan-Fryns syndrome and polymorphisms in the gene have been associated with SCZ and psychosis. Interestingly, several other ID genes encode subunits of the mediator: *CDK8*, *MED17*, and *MED23*.

The number of transcription factors and epigenetic regulators associated with normal and impaired intelligence is rapidly growing and extensive protein-protein interactions and regulatory crosstalk can be recognized between these. For example, interactions have been demonstrated between the transcription factor Ying Yang 1 (YY1) and the histone deacetylase SIRT1 to regulate expression of CREB. YY1 also interacts with MECP2, which may contribute to illegitimate depression of D4Z4-associated genes in facioscapulohumeral muscular dystrophy (128). Many more ID genes encoding transcription regulators will be identified and the challenge for the coming years will be to establish a comprehensive view of the functional interactions between those proteins and to identify the neuronal targets that may be commonly affected by ID-associated mutations.

PROSPECTS FOR THERAPY

For a long time, ID and ASD have been considered as neurodevelopmental disorders with irreversible cognitive deficits. However, this view has been changing over the past few years thanks to increasing knowledge about the genetic and molecular basis of these conditions and because of the generation of powerful animal models. These studies have raised hope that, at least in some cases, neurological effects of single gene mutations can be ameliorated during adulthood. The best known example of successful adult rescue of a learning and memory deficit has been obtained for fragile X syndrome. The FMRP protein regulates local protein translation upon stimulation of mGLUR5 receptors; however, because of the mutation this translational control is lost and illegitimate translation occurs in the absence of stimuli. In a fly model for fragile X syndrome, the absence of FMRP results in structural defects of the mushroom body and leads to impaired learning and memory in courtship behavior. Interestingly, application of several mGLUR5 antagonists, such as MPEP and lithium in the food of adult flies, could restore memory performance in the courtship behavior paradigm, whereas structural defects of the mushroom body remained (90). These promising results were subsequently recapitulated in fragile X mouse models (143), and clinical trials in fragile X syndrome patients based on these data are currently in progress. Improvement of the neurological defects was also achieved by conducting a gene rescue at the adult stage in a mouse model of Rett syndrome (Mecp2) (51) and a *Drosophila* model of Kleefstra syndrome (EHMT) (78), suggesting that treatment of IDs with a different genetic etiology is in theory feasible. Although gene therapy and cell therapy are being considered for neurodegenerative disorders, such as Parkinson's disease, in which

specific cell populations are affected, it seems unlikely that such strategies will be generally feasible in ID because of the potential safety risks and the lack of a specific target area in the brain. The relatively rare involvement of individual genes in most ID conditions is another problem for the development of therapeutic strategies. It is commercially uninteresting to design single gene–based therapeutic interventions. However, as we have seen, many ID genes converge onto common molecular and cellular pathways, suggesting that drugs targeted toward these pathways could have a beneficial effect for a much larger group ID disorders. Knowledge-based analysis of compounds that have an effect on general neuronal mechanisms has revealed beneficial effects toward the neurological phenotype in animal models, and in some cases clinical trials in ID patients have already been initiated based on these results. The main pathways and processes that are targeted by these drugs are synapse structure and plasticity (90, 143), modification of chromatin structure, Ras and Rho signaling pathways (72, 76), and PI3K-mTOR translational control (43). Interestingly, the very same pathways have been intensively studied for their role in tumor development and progression, and a wide variety of compounds have already been identified that can correct effects of disrupted players within these pathways. Thus, many compounds affecting Ras signaling or chromatin modifications are already known and in some cases used in clinical practice. Such FDA-approved drugs can be repurposed to test their ability to rescue phenotypic features in animal models and in ID patients.

Histone deacetylase (HDAC) inhibitors enhance memory processes by the activation of key genes regulated by the CREB-CBP transcriptional complex and have been shown to alleviate memory deficits in a mouse model for Rubinstein-Taybi syndrome (132). HDAC inhibitors, such as trichostatin A and valproic acid, do not globally alter gene expression but instead increase the expression of specific genes during memory consolidation and therefore may be attractive for treatment of other IDs in which epigenetic regulation is disrupted. Valproic acid, which is widely used as an antiepileptic drug, has been tested for its potential to reactivate *FMR1* gene expression and reverse symptoms in fragile X syndrome patients (124). Preliminary results suggested a beneficial effect toward the features of ADHD in young patients, which warrant further investigation. Modulation of Ras activity by farnesyltransferase inhibitors and by HMG-CoA reductase inhibitors showed improved cognitive functioning in a mouse model for NF1 (31). Based on these results, the HMG-CoA inhibitor simvastatin was tested in a cohort of 114 NF1 children (76), which did not reveal a general improvement of cognitive function. However, simvastatin-treated children performed considerably better in an object assembly test than placebo-treated children, and therefore further trials are warranted in NF1 and other disorders involving disrupted Ras/MAPK/ERK signaling. Finally, modulation of PI3K-mTOR signaling downstream of the Ras pathway is emerging as another therapeutic target for several types of ID, including tuberous sclerosis and ASD. Rapamycin can restore the disruption of the PI3K-mTOR pathway (TOR stands for target of rapamycin) and has the capacity to improve cognitive deficits in *Tsc1* and *Tsc2* knockout mice, even in adult animals (43).

Obviously, more basic and translational research will be required to find the most suitable drugs and their optimal dosage for highest efficacy with the fewest side effects. In addition, it would be unreasonable to expect that one could restore normal intelligence in patients with severe ID. Nevertheless, the above examples provide proof of concept that improvement of symptoms, including intellectual impairment, is not impossible for some forms of ID and therefore raise hope that modulation of underlying common pathways by drugs can become a realistic approach to improve the quality of life for patients and families confronted with these conditions.

SUMMARY POINTS

1. IDs represent a large and heterogeneous group of disorders. Patients have variable degrees of intellectual impairment and social and behavioral adaption problems. A wide variety of chromosomal aberrations and a bewildering number of single gene mutations may cause ID.
2. IDs share a common etiology with other CDs such as ASDs and SCZ. This can be deduced from the high cooccurrence of these conditions and from the fact that isolated manifestations of these conditions may involve mutations and polymorphisms in the same genes.
3. The increasing power of sequencing allows the elucidation of causative genetic defects and risk factors in CD by analysis of entire exomes and soon complete genomes, which will have a considerable impact on diagnostic testing. The resulting complete landscape of all CD-associated genes will further stimulate fundamental neurobiological research.
4. Extensive functional interactions are seen between the corresponding protein products of ID genes, indicating that individual ID genes converge onto a more limited number of common molecular and cellular pathways.
5. Mutations in many different types of ID, autism, and SCZ affect synaptic morphology and plasticity. Epigenetic control of neuronal gene expression is also commonly affected.
6. Although ID and other CDs have a neurodevelopmental origin, studies with model organisms show that neurological defects can be rescued at least in part at the adult stage. These observations offer promising perspectives for possible therapy.

FUTURE ISSUES

1. How many genes will give rise to mild or severe ID when mutated?
2. To what extent will oligogenic or polygenic inheritance models and epistasis contribute to the prevalence of mild ID?
3. What is the relationship between polymorphisms that affect ID genes and IQ level?
4. Can we really modulate pathways that are commonly affected in ID to ameliorate (neurological) symptoms in a safe and effective way?

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RELATED RESOURCES

1. EURO-MRX. 2010. The European Mental Retardation Consortium. **http://www.gencodys.eu/**
2. Greenwood Genetic Center XLID Update of the Atlas on X-Linked Mental Retardation. 2011. **http://www.ggc.org/research/molecular-studies/xlid.html**
3. Online Mendelian Inheritance in Man, OMIM®. 2011. Baltimore, MD: McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University. **http://omim.org/**
4. S2D. 2011. Synapse to Disease project. **http://www.synapse2disease.ca**
5. GENCODYS. 2011. Genetic and Epigenetic Networks in Cognive Dysfunction. **http://www.gencodys.eu/**

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