Published in final edited form as:
Neurosci Biobehav Rev. 2014 October ; 46 Pt 2: 161–174. doi:10.1016/j.neubiorev.2014.02.015.

Intellectual Disability and Autism Spectrum Disorders: Causal Genes and Molecular Mechanisms

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Abstract

Intellectual disability (ID) and Autism Spectrum disorder (ASD) are the most common developmental disorders present in humans. Combined, they affect between 3-5% of the population. Additionally, they can be found together in the same individual thereby complicating treatment.

The causative factors (genes, epigenetic and environmental) are quite varied and likely interact so as to further complicate the assessment of an individual patient. Nonetheless, much valuable information has been gained by identifying candidate genes for ID or ASD. Understanding the etiology of either ID or ASD is of utmost importance for families. It allows a determination of the risk of recurrence, the possibility of other comorbidity medical problems, the molecular and cellular nature of the pathobiology and hopefully potential therapeutic approaches.

Keywords

Intellectual Disability; Autism Spectrum Disorders; Synaptic plasticity; Neurodevelopmental disorder; Molecular pathways

Introduction

Intellectual disability (ID) and Autism Spectrum Disorders (ASDs) are major social problems in all countries. Each, individually, have a rather high prevalence, with ID affecting 1-3% of the population and ASDs is found in 1/50 school age children (Perou et al., 2013). Both conditions are heterogeneous, thereby posing an immense challenge to the clinical geneticist in search of a diagnosis for the patient and their family in need of genetic counseling to determine recurrence risks.

Intellectual disability is a condition characterized by below average intellectual functioning (IQ<70) in conjunction with significant limitations in adaptive functioning. Intellectual disability may occur as an isolated phenomenon or accompanied with malformations, neurological signs, impairment of the special senses, seizures and behavioral disturbances. Autism spectrum disorder comprises a group that includes autistic disorders, Asperger syndrome, pervasive developmental disorder not otherwise specified (PDD-NOS) and Rett

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Syndrome (American Psychiatric Association, 2000). Patients with ASDs share features of restrictive and repetitive behaviors, dysfunctional reciprocal social behavior, and impaired communication abilities (Wilkins and Matson, 2009).

Besides the heterogenecity of ID and ASDs, they are extremely likely to be related biochemically and molecularly. Both exist together in the majority of patients. Seventy percent of individuals with ASDs have some level of ID while the remaining 30% have some disability (speech, behavior) other than cognitive dysfunction (Mefford et al., 2012; Newschaffer et al., 2007; Wilkins and Matson, 2009). Conversely, at least 10% of individuals with ID have ASDs, with some ID conditions exhibiting a much higher level of co-morbidity.

The genetic causes for ID and ASDs are quite varied and similar. Single gene mutations, as well as copy number variants (CNVs), either duplications or deletions, are associated with both conditions. Additionally, hypomorphic alterations in multiple genes suggesting an oliogenic mode of inheritance have recently been noted for both conditions. Recently, large-scale whole exome sequencing (WES) studies found that no single gene was significantly associated with ASD risk. Rather a likely contribution of rare risk variants scattered across hundreds of genes was speculated (Anney et al., 2012; Liu et al., 2013). The same mutation or CNV gives rise to either ID or ASDs and variations within a large number of these genes, for example, *NRXN1*, *CNTNAP2*, *NLGN4*, *SHANK2* and *SHANK1*, have been found to be associated with ID as well as ASD (Berkel et al., 2010; Sato et al., 2012; Kim et al., 2008; Laumonnier et al., 2004; Zweier et al., 2009). These observations further substantiate the involvement of similar cellular and molecular processes and indicate the role of environment and genetic background plays in the expression of ID (Figure 1) and probably ASD.

Many rare and inherited mutations in ASD-associated genes often display incomplete penetrance. Most pathogenic mutations in the known ASD-associated genes and in a majority of ID genes have a very low prevalence in their respective patient populations. Thus the diagnostic application and understanding of the molecular mechanisms underlying ID and ASD remain limited.

Much time and effort by multiple groups throughout the world have been devoted to identifying specific genetic causes for ID and ASDs. As a result of these efforts, at least 400 genes have been found to be associated with each of these entities (reviewed in van Bokhoven 2011). However, it is highly probable this number only represents a minor proportion of genes involved. For examples, with respect to ID, 400 genes may account for a fourth of the genes involved based on the number of known X-linked intellectual disability genes is presently about 100, and the X chromosome accounts for about 1/20 of the human genome.

It is hypothesized that primary causative factors (monogenic causes, epigenetic and environmental factors or other as yet unidentified causative factors) do not directly result in cognitive impairment. Rather, the mutant genes or other primary causative factors directly or indirectly cause metabolic disruptions, altered neurodevelopment and interference in cell proliferation and/or migration, which then lead to the brain abnormalities that result in

cognitive and behavioral disabilities. It is likely that common groups of genes, proteins and metabolites or a combination of these are affected in either a majority or subset(s) of ID patients.

Although screening of patients with ID or ASD has indeed identified viable candidate genes involved in these phenotypes, the process is laborious and, as already mentioned, quite incomplete. The number of genes is vast and the number known small. Components of common interaction networks and biological processes associated with these genes/proteins are likely critical and unique to normal cognitive and behavioral function. Therefore other approaches have been undertaken to better understand the etiologies of these conditions. One very productive approach has been that of system biology. Kou et al (2012) used a combined network and systems biology approach to predict candidate genes for ASD and ID. Their results were quite interesting in that they were able to slow both conditions shared common pathways and had similar clusters of genes which was comforting as this was not unexpected based on the accumulating evidence alluded to before. Importantly, using these interconnected pathways, as one begins to understand ID one may then also better understand ASD and visa versa.

Cristino et al. (2013) used a similar network approach, a hypothetical ‘gene network model’ based on candidate genes and associated protein – protein interaction networks, to build protein modules containing about 4,000 genes which might contribute to neurodevelopmental and neuropsychiatric disorders. Their data were in agreement with previous approaches in their identification of molecular pathways, functional domain and gene regulation. However, their findings also contained some novel insights. Their analysis, by including variants identified in genome wide association studies found regulatory regions for transcription factors (TF) and miRNA, located in the 5’ upstream regulatory regions and the 3’ UTR of genes. These, in turn, identified candidate genes and miRNA target sites. At the end, Christino et al. (2013) found that the TFs in a network regulated other genes in the network and the genes were enriched for miRNA sites.

Genes Linked to ID and ASD

Functional categorization of proteins encoded by a majority of ID and ASD-associated genes and elucidation of common pathways has become crucial not only for the understanding of cellular and molecular mechanisms underlying pathophysiology of these genes but also in assessing the potential pathogenicity of new candidate genes for ID and ASD. Such a functional categorization has led to emergence of diverse cellular functions influencing neuronal structure and functions that are affected by defects in the ID and ASD genes. For example, successes in delineating the molecular basis for XLID have led to the elucidation of genetic mechanisms for specific XLID disorders and provided valuable insights into fundamental aspects of neuronal function that are involved in normal development of human cognition. These functions include but are not limited to transcription and translation regulation, protein modification, chromatin remodeling, actin cytoskeleton assembly involving neurite outgrowth, and cellular processes including RNA splicing, translation, energy metabolism, transport of small molecules, nonsense mediated decay of mRNA, and disturbances in ubiquitination. Furthermore, the identification of

interacting partners of ID and ASD gene products and targets of known ID and ASD genes has led to the elucidation of specific pathways linked to ID and ASD. Many ID and ASD genes appear to convergence onto common pathways. One common theme that has emerged recently is that a significant number of ID and ASD-linked proteins are synaptic molecules and directly or indirectly affect structure and function of neurons, more specifically dendrites and synapses.

Several classes of molecules participating in various cellular processes and thus regulating neuronal morphology and communication are found to be critical for normal cognition and behavior function and defects in these molecules cause ID and ASD. These include molecules present at synapses and regulating synaptic vesicle transport, neuronal cytoskeleton dynamics, maintaining synaptic contacts such as cell surface receptors, cell adhesion molecules, postsynaptic density proteins, molecules influencing transcriptional regulation and chromatin remodeling, and molecules involved in maintaining synaptic protein level are found to be major factors in the causation of ID. Here we will focus on ID and ASD-associated molecules, pathways and abnormal cellular processes affecting neuronal morphology and function (Table 1). Figure 2 exemplifies the complexity of the synaptic compartments illustrating the selected molecules and pathways implicated in ID and ASD.

Neuronal morphology, synaptic plasticity and cognitive disorders

In the human brain, processing and transmission of information in the form of electrical signals are carried out by a trillion (10^{12}) neurons and a quadrillion (10^{15}) synapses. Synapses are adhesive junctions highly specialized for mediating communication between neurons in the brain. Most of the chemical synapses consist of three components: presynaptic axon terminals, a synaptic cleft, a gap of 20-25 nm between pre-and postsynaptic compartments, and postsynaptic dendritic regions (Bourne and Harris, 2008; Ho et al., 2011). Most neurons consist of morphological distinct regions such as single axons harboring presynaptic terminals that represent the information output centers and several dendrites bearing synapses, both excitatory and inhibitory, representing centers for information input. The dendrites of most neurons are covered with small protrusions known as dendritic spines. Structurally, spines have a long thin neck and a head that contains the excitatory synapse (Bourne and Harris, 2008). The inhibitory synapses are predominantly formed on the neuronal cell bodies and dendritic shafts (Bourne and Harris, 2008).

Communication at synapses involves the release of chemical neurotransmitters from the presynaptic terminals in response to electrical impulses (i.e. action potentials), diffusion across the synaptic clefts, and binding to postsynaptic receptors (Cesca et al., 2010; Ho et al., 2011). The postsynaptic compartment in turn converts these chemical signals back into action potentials, allowing their propagation. The presynaptic terminals contain synaptic vesicles filled with neurotransmitters and a dense matrix of cytoskeleton and scaffolding proteins at the site of neurotransmitter release, the active zone (Ho et al., 2011; Waites and Garner, 2011). A wide-variety of cell-adhesion molecules holds pre- and postsynaptic regions together at the proper distance through trans-synaptic interactions (Missler et al., 2012). Spines and synapses are highly dynamic in their morphology and can undergo rapid

structural changes in response to stimuli. This property is called synaptic plasticity. Changes in the morphology of spines underlie long-term potentiation (LTP) and long-term depression (LTD), two processes that model the activity-dependent changes of synaptic strength and which are considered to represent the cellular basis of learning and memory.

Synapse formation is a highly complex process, which is orchestrated in a precise temporal and spatial manner during early development and in adult brain. Development of synapses can be divided into four specific steps: neurite outgrowth i.e. axons need to find their targets cells, and dendrites need to be elaborated to provide target fields for synapse formation; contact between axonic presynaptic terminals and dendrites' postsynaptic terminals; synapse elimination that refines the accuracy of circuit formation/neuronal connectivity patterns; and finally the functional balance between excitatory and inhibitory synapses is modulated through regulation of both synapse number and function. Synaptic connectivity that is regulated by the formation and elimination of synapses is found to be critical for learning, memory and behavior function in the developing and adult brain.

The current understanding of the cellular and molecular mechanisms of neuronal morphology and synaptic transmission has come from studies on the hippocampal and cortical pyramidal neurons. Subtle changes in dendritic or synaptic structure can ultimately lead to enormous changes in information processing. Recent evidence suggests that dendritic branches and spines are key regulators of neuronal function and essential for the formation and plasticity of neuronal circuits, and are disrupted in many neurodevelopmental disorders such as ID and ASD in which behavioral and intellectual functions are affected (Auerbach et al., 2011; Durand et al., 2012; Holtmaat and Svoboda, 2009; Hutsler and Zhang, 2010; Jan and Jan, 2010; Kaufman et al., 2010; Sudhof, 2008; Tsai et al., 2012; Valnegri et al., 2012).

A large body of evidence indicates dysfunction of the synapse (synapse formation and plasticity) and dendrites as major contributing factors in ID and ASD. A consistent feature of neurons in patients with ID is abnormal dendritic structure and/or alterations in dendritic spine morphology (Blanpied and Ehlers, 2004; Huttenlocher, 1974; Irwin et al., 2001; Kaufmann and Moser, 2000; Purpura, 1974). Post-mortem analysis of human ID brain tissue often shows dendritic spines with altered shapes and densities. Altered spine morphology has been observed in post-mortem cortical tissue from patients with ASD (Hutsler and Zhang, 2010). Defects in dendritic spine morphology are also consistently found in mouse models for several ID and ASD genes (Belichenko et al., 2004; Clement et al., 2012; Comery et al., 1997; Wang et al., 2011). Most of the ID/ASD-related proteins have been shown to be enriched at pre- and/or postsynaptic compartments and have been found to affect both dendrite and spine structures in number and morphology linked to the control of neuronal structure and connectivity (Humeau et al., 2009). The finding of many independent, individually rare genetic variants in synaptic proteins implicates a role of synaptic cell-adhesion pathways in cognitive and behavior function (Betancur et al., 2009; Glessner et al., 2009; Valnegri et al., 2012). Recently, a role for ubiquitination and protein degradation in synaptic function and neurodevelopmental disorders such as ID and autism has also been identified (Mabb and Ehlers, 2010). Many genes from the ubiquitin pathway and neuronal proteins that are targeted by the unbiquitin-proteasome system have been linked to cognitive defects (Glessner et al., 2009; Lehman, 2009; Salinas et al., 2006). It is

further evident that multiple ID- and ASD-associated genes are involved in activity-dependent synapse elimination that refines the accuracy of neuronal circuit formation (Pfeiffer et al., 2010; Tsai et al., 2012). Studies involving many of the synaptic genes have shown the significance of any causal rare variant in ID or ASDs (Gilman et al., 2011). A network-based analysis of genes affected by rare de novo CNVs in autism suggested that perturbed dendritic morphogenesis and synaptogenesis are the key to autism (Gilman et al., 2011). Several studies suggest that the changes in neuronal gene expression controlled by selective expression of transcription factors affect the formation of dendritic spines and synapses (Ben-David and Shifman, 2012; Ebert and Greenberg, 2013; Voineagu et al., 2011; West and Greenberg, 2011).

Regulation of cytoskeleton dynamics

The structure and dynamics of dendrites and spines have been shown to be influenced by the underlying actin-cytoskeleton. The cytoskeleton forms the backbone of neuronal architecture and is critical for axon outgrowth and synapse formation. Once synapses have been formed, the neuronal cytoskeleton supports their maintenance and maturation and thus the synaptic cytoskeleton is essential for stabilization and remodeling of synaptic connections (Dent et al., 2011). Actin filaments are the predominant cytoskeletal element in dendritic spines whereas actin and microtubules constitute cytoskeleton of dendrites (Fifkova and Delay, 1982; Hoogenraad and Bradke, 2009; Matus et al., 1982). Both formation and reorganization of spines are accompanied by dynamic rearrangements of actin filaments (Matus, 2000; Rex et al., 2010). Inhibition of actin polymerization attenuates LTP maintenance, whereas LTD is associated with actin filament disassembly (Okamoto et al., 2004). Signaling molecules and pathways that regulate actin-cytoskeleton organization have a major impact on the structure and function of dendrites and spines. Key molecules mediating changes in these structures are actin-binding proteins and members of the family of small Rho GTPases such as, RhoA, Rac, and Cdc42 (Hotulainen and Hoogenraad, 2010). These proteins play important roles in synaptic functions, dendritic branching, dendritic spine formation and maintenance, and neurite outgrowth and differentiation.

Rho GTPases function as molecular switches, cycling between an inactive GDP-bound state and an active GTP-bound state. The activity is regulated by positive regulators (guanine nucleotide exchange factors, GEFs), negative regulators (GTPase activating proteins, GAPs) and by guanine nucleotide disassociation inhibitors (GDIs) (Ba et al., 2013; Govek et al., 2004). Several genes implicated in ID and ASD code for proteins associated with GTPase signaling and function as regulators or effectors of Rho GTPases or Rac and Cdc42. These genes include OPHN1, MEGAP, OCRL1, ARHGEF6, ARHGEF9, FGD1, LIMK1, PAK3, and IQSEC2.

The ID gene *OPHN1* encodes oligophrenin 1, a Rho GTPase activating protein (Rho-GAP), expressed both pre- and postsynaptically in neurons e.g. in axons, dendrites and spines and plays role in the activity-dependent maturation and plasticity of excitatory synapses by regulating their structural and functional stability (Nadif Kasri et al., 2009). Oligophrenin 1 was found to negatively regulate RhoA and interact with the post-synaptic protein Homer and knock-down of oligophrenin-1 levels in CA1 neurons in rat hippocampal slices resulted

in significantly decrease spine length (Govek et al., 2004). Recently it was shown that synaptic activity through NMDA receptor activation drives OPHN1 into dendritic spines, where it forms a complex with AMPA receptors, and selectively enhances AMPA-receptor mediated synaptic transmission and spine size by stabilizing synaptic AMPA receptor, suggesting that normal activity-driven glutamatergic synapse development is impaired by perturbation of OPHN1 function (Nadif Kasri et al., 2009).

PAK3, an XLID protein, is a member of the large family of p21-activating kinases (PAK), which are downstream effectors for Rac and Cdc42 (Allen et al., 1998; Kreis et al., 2007; Rousseau et al., 2003). Activation of PAK by Rac1 or Cdc42 leads to the activation of LIMK1, which in turn phosphorylates and inactivates cofilin, a crucial modulator of actin dynamics (Arber et al., 1998; Edwards et al., 1999). Down regulation of PAK3 results in morphological spine abnormalities, including an increased proportion of abnormally elongated, thin and immature spines, and variable defects in synaptic plasticity (Boda et al., 2004; Dubos et al., 2012; Meng et al., 2005). PAK3-knockout mice have impaired synaptic plasticity and cognitive function, and mice lacking LIMK1, a gene considered to be causative for the neurological features of Williams-Beuren syndrome with mild-severe ID, showed abnormalities in synaptic function and impaired fear conditioning and spatial learning (Meng et al., 2005; Meng et al., 2002). Recent studies showed that PAK3 is specifically recruited in the spine head of activated spines. Additionally, researchers found a small reduction of PAK3 in the nearby dendrite as opposed to more distal parts of the dendrite. This result therefore suggests that the redistribution of PAK3 relieves its negative action on spine growth in the nearby dendrite and thereby promotes a local formation of new spines, as seen with PAK3 inhibition (Dubos et al., 2012).

Other ID proteins, FGD1, ARHGEF9 (collybistin) and ARHGEF6 (αPIX) are GEFs. ARHGEF9 and FGD1 are specific for Cdc42, while ARHGEF6 activates both Rac1 and Cdc42. *ARHGEF9*, which encodes a Cdc42 GEF protein collybistin, is specifically enriched in neuronal dendrites, and involved in the formation of inhibitory synapses (Kneussel et al., 2001a; Kneussel et al., 2001b; Papadopoulos et al., 2007; Tyagarajan et al., 2011). Collybistin is essential for the clustering of the postsynaptic scaffold protein gephyrin and along with Cdc42 regulates GABAergic postsynaptic densities (Korber et al., 2012; Tyagarajan et al., 2011). ARHGEF6, which was initially isolated as a PAK interacting protein, localizes specifically at the post-synaptic compartment of excitatory synapses (Node-Langlois et al., 2006). Knockdown of the rat *Arhgef6* in cultured hippocampal neurons resulted in abnormalities in spine morphology similar to those reported with knockdown of PAK3. This phenotype could be rescued by a constitutively active form of PAK3 (Node-Langlois et al., 2006). *Arhgef6* knockout mice exhibited an increase in both dendritic length and spine density, accompanied by an overall loss in spine synapses and showed a dramatic reduction in the levels of the active Rac1 and Cdc42 in the hippocampus (Ramakers et al., 2012).

IQSEC2 is a guanine nucleotide exchange factor for the small GTPase, ADP-ribosylation factor 6 (ARF6), which localizes to the postsynaptic density of excitatory synapses (Shoubridge et al., 2010a; Shoubridge et al., 2010b). ARF6 is known to regulate endosomal trafficking and actin dynamics (D'Souza-Schorey and Chavrier, 2006; Grant and Donaldson,

2009). ARF6 mediates mobilization of TLN (TLN/intercellular adhesion molecule-5 (ICAM5)), which localizes to dendritic filopodia. The endocytosis of TLN affects filopodia-to-spine transition, and requires Rac1-mediated dephosphorylation/release of actin-binding ERM proteins from TLN (Raemaekers et al., 2012).

Presynaptic vesicle cycling and exocytosis

Formation of a chemical synapse requires exchange of organizing signals between the synaptic partners. Pre- and postsynaptic specializations form in precise opposition to each other at sites where axons contact specific target cells. Neurotransmitters such as glutamate or ρ-aminobutyric acid (GABA) are made by the presynaptic neurons and stored in synaptic vesicles at presynaptic terminals. A critical step in presynaptic differentiation is the clustering of synaptic vesicles near neurotransmitters release sites, the active zone, where vesicle fusion and exocytosis of neurotransmitters occur (Sudhof, 2004). Several presynaptic molecules involved in the regulation of synaptic vesicle release that involves a multistep process including, vesicle endocytosis (transport/mobilization), docking, priming, fusion, and recycling, have been identified and are found to be defective in ID and ASD.

The synapsins (Syns) are a family of neuron specific phosphoproteins, which localize in the presynaptic compartments and interact with each other, actin and with the cytosolic surface of SVs (reviewed in Cesca et al. 2010) They help maintain a reserve pool of vesicles by tethering SVs to each other and to actin to regulate the availability of SVs for release through their phosphorylation-dependent dissociation from SVs and actin and to play a role in the post docking step of exocytosis (Baldelli et al., 2007; Chi et al., 2001, 2003; Chiappalone et al., 2009). *SYN1* mutations are associated with epilepsy and/or autism (Fassio et al., 2011; Giannandrea et al., 2013). Neurons from single or multiple Syn knockout mice show impairment in inhibitory neurotransmission and enhancement in excitatory transmission, accompanied by alteration in synaptic plasticity. A selective decrease in the density of SVs is noted in nerve terminals i.e. presynaptic compartments. It was noted that in the absence of Syns, SVs show higher mobility and become dispersed along axons (Fornasiero et al., 2012; Orenbuch et al., 2012). Lack of Syn1 and/or Syn11 triggers a strong epileptic phenotype in mice associated with cognitive impairments (Greco et al., 2013).

αGDI (GDP-dissociation inhibitor), an XLID protein, encoded by the *GDI1* gene, controls the cycling of RAB GTPases that act as molecular switches between the active GTP-bound and inactive GDP-bound state and are involved in intracellular vesicle trafficking (Takai et al., 2001). GDI1 knockout mice exhibit a large decrease in the reserve pool of SVs and short-term memory deficit (Bianchi et al., 2009; Bianchi et al., 2012). Mutations in another small GTPase gene, RAB39B, cause XLID associated with autism, epilepsy, and macrocephaly (Giannandrea et al., 2010). Its downregulation leads to an alteration in the number and morphology of neurite growth cones and a significant reduction in presynaptic compartments and supports the importance of the intracellular trafficking mediated by the αGDI-RAB pathway in cognitive and behavioral function.

The most critical step of exocytosis, SV fusion with the presynaptic membrane, is mediated by the SNARE (soluble N-ethymalemide sensitive factor attachment protein receptor)

complex composed of three SNARE proteins, syntaxin, SNAP-25, and synaptobrevin and Munc18-1 (Pevsner et al., 1994; Sollner et al., 1993). Munc18-1 is encoded by the STXBP1 gene that is found to be mutated in cases with nonsyndromal ID and ID with epilepsy (Hamdan et al., 2011; Milh et al., 2011). Munc18-1 has been ascribed a variety of functions in exocytosis and has been shown to promote vesicle priming, SNARE complex assembly, trafficking of syntexin1 to the plasma membrane, by preventing the formation of ectopic SNARE complexes (Kong et al., 2013; Smyth et al., 2013; Zhou et al., 2013).

Defects in *IL1RAPL1* have been associated with ID and autism (Bhat et al., 2008; Carrie et al., 1999; Piton et al., 2011; Piton et al., 2008). IL1RAPL1 belongs to the Toll/IL-1 Receptor family and interacts with neuronal calcium sensor-1 (NCS-1) and inhibits calcium-dependent exocytosis, neurotransmitter release and NGF-induced neurite elongation (Bahi et al., 2003; Gambino et al., 2007). Pavlowsky and coworkers identified PSD-95 as a novel partner of IL1RAPL1 and showed that it regulates dendritic spine number and PSD-95 localization to excitatory synapses by controlling c-jun terminal kinase (JNK) activity and PSD-95 phosphorylation (Pavlowsky et al., 2010a; Pavlowsky et al., 2010b).

Through trans-synaptic interaction with presynaptic protein phosphatase (PTP) δ, IL1RAPL1 has been found to mediate synapse formation (Yoshida et al., 2011). Recently, IL1RAPL1 has been shown to interact with Mcf2-like (Mcf2l), a Rho guanine exchange factor, through the cytoplasmic Toll/IL-1 receptor domain and regulates the formation and stabilization of glutamatergic excitatory synapses of cortical neurons through RhoA signaling (Hayashi et al., 2013).

Synaptic vesicle recycling is required for effective synaptic transmission. The family of adaptor protein (AP) complexes, AP-1, AP-2, AP-3 and AP-4, mediates various types of vesicle formation (Robinson, 2004). Adaptor protein complexes are evolutionary conserved hetrotetrameric complexes that mediate different types of vesicle formation and the selection of cargo molecules for inclusion into these vesicles. Synaptic vesicle recycling involves AP-2/clathrin mediated endocytosis. Mice deficient in the tissue specific AP-1-σ1A complex showed impaired synaptic vesicle recycling in the hippocampal synapse (Glyvuk et al., 2010). Mutations in genes encoding AP4 complex subunits (AP4B1, AP4E1, and AP4S1) have been identified in patients with ID, progressive spastic paraplegia, shy character, and short stature (Abou Jamra et al., 2011). Mutations in AP4M1 and AP4E1 have recently been found in patients with cerebral palsy associated with severe ID (Abou Jamra et al., 2011; Kong et al., 2013; Moreno-De-Luca et al., 2011)

In addition, *SYP*, which encodes synpatophysin, an integral membrane protein found in transport vesicle and interacts with synaptobrevin, an essential component of SNARE complex, is found to be mutated in cases with nonsyndromal ID and ID with epilepsy (Tarpey et al., 2009). At the presynaptic site, reduced or defective OPHN1 signaling has been shown to impair synaptic vesicle (SV) cycling at hippocampal synapses. It forms a complex with endophilin A1, a protein implicated in membrane curvature generation during SV endocytosis (Nakano-Kobayashi et al., 2009).

CASK, another XLID gene, encodes a calcium/calmodulin-dependent serine protein kinase that is a member of the membrane-associated guanyl kinase (MAGUK) family of scaffolding proteins (Hackett et al., 2010; Hsueh, 2006; Najm et al., 2008). CASK binds to the cytoplasmic tails of the presynaptic cell adhesion molecules β-neurexin (Sun et al., 2009). Mutations in neurexin 1 have been linked to ID. CASK also binds to the cytoplasmic domain of KIRREL3, a presynaptic cell adhesion molecule implicated in autosomal ID (Bhalla et al., 2008). The functional implication of this interaction has yet to be elucidated. Recently, liprin-α2, which is required for regulating synaptic vesicle pool size, has been shown to be critical for recruitment of several components of the vesicle release machinery, including CASK (Spangler et al., 2013).

Translational regulation, protein degradation and turnover

It is quite evident that synaptic proteins are critical for learning, memory and behavioral functions. Several studies have suggested tight regulation of protein translation and degradation is critical in neurodevelopment. It is well established that de novo protein synthesis has an important function in synaptic transmission and plasticity (Cajigas et al., 2010). Recently, several studies have highlighted an important function for protein degradation by the ubiquitin proteasome system (UPS) in synaptic plasticity (Mabb and Ehlers, 2010; Segref and Hoppe, 2009; Tai and Schuman, 2008). These observations suggest that changes in synaptic transmission involve extensive regulation of the synaptic proteome.

The synaptic proteome is also affected by the nonsense-mediated mRNA decay (NMD) pathway that provides a translation-coupled quality control system. The NMD functions not only in degrading aberrant mRNAs with a premature termination codon (PTC) but also in regulating the transcriptome (reviewed in Nguyen et al. 2013a). Mutations and CNVs in several NMD-associated genes, *UPF3B*, *UPF3A*, *SMG6*, *EIF4A3*, *RNPS1*, and *RBM8A*, have been shown to be likely causes or predisposing factors for neurodevelopmental disorders such as ID, autism and ADHD. (Addington et al. 2011; Jolly et al. 2013; Laumonnier et al. 2009; Nguyen et al. 2012, 2013b; Tarpey et al. 2007b).

The UPS comprises a group of enzymes, an ubiquitin-activating enzyme (E1), an ubiquitin-conjugating enzyme (E2), and an ubiquitin ligase (E3), that activates and then attaches a 76 amino acid protein ubiquitin to lysine residues of specific substrates. Thus, ubiquitination post-translation ally modifies protein function and triggers the subsequent degradation of ubiquitinated proteins by the 26S proteasome. Various components of the multicomplex UPS are necessary for proper development of the brain, axon outgrowth and guidance, synapse development and plasticity. It has been shown that protein degradation through the UPS controls proper synaptic balance by maintaining optimal protein levels, thus promoting functional equilibrium (Bingol and Schuman, 2006; Cajigas et al., 2010; Ehlers, 2003). Several studies have revealed a crucial role of the UPS in the spatial and temporal control of protein turnover in the nervous system, which regulates the development and maintenance of specialized neuronal structures, and consequently , neuronal transmission. Thus, it is not surprising that a growing group of ID linked proteins are directly involved in UPS-mediated protein degradation such as UBE3A, UBE2A, UBE3B, HUWE1, MID1, CUL4B, and UBR1 (Badura-Stronka et al., 2010; Basel-Vanagaite et al., 2012; Budny et al., 2010; Flex et al.,

2013; Froyen et al., 2008; Hwang et al., 2011; Isrie et al., 2013; Kishino et al., 1997; Matsuura et al., 1997; Nascimento et al., 2006; Tarpey et al., 2007; Zenker et al., 2005; Zou et al., 2007).

Maternally inherited loss-of-function mutations in *UBE3A* cause Angelman syndrome (AS), a neurodevelopment disorder characterized by the absence of speech, movement ataxia, excessive laughter, and severe cognitive impairment (Kishino et al., 1997; Matsuura et al., 1997). Mutations of *UBE3A* have also been found to be associated with ASDs (Glessner et al., 2009). UBE3A localizes to dendrites and spines, and its absence in mice leads to reduced spine density and length and defects in synaptic plasticity (Dindot et al., 2008; Yashiro et al., 2009). UBE3A encodes an ubiquitin E3 ligase, also known as E6-associated protein (E6-AP), containing the C-terminal HECT domain that catalyzes the ubiquitination of target proteins. Recently, it was shown that Ube3A regulates excitatory synapse development by controlling the degradation of Arc, a synaptic protein that promotes the internalization of the AMPA subtype glutamate receptors (Greer et al., 2010). Mice deficient in maternal Ube3A express elevated levels of Arc in response to synaptic activity, which coincides with severely impaired LTP in the hippocampus and the deficit in learning behaviors. The authors suggested this deregulation of AMPA receptor expression at synapse may contribute of cognitive dysfunction that occurs in Angelman syndrome and possibly ASDs. Recently, TrkB receptor signaling, which is known to be essential for both the induction and maintenance of LTP, was also found to be defective as result of elevated Arc levels in the AS mouse (Cao et al., 2013). However, a recent report suggests that Arc is not a direct target substrate for UBE3A and the authors provide evidence that Arc protein levels are rather controlled by UBE3A at the transcription rather than at posttranscriptional level (Kuhnle et al., 2013).

Several genes in the ubiquitin pathways, including *UBE3A*, *PARK2*, *RFWD2*, and *FBOX40* were found to be affected by CNVs enriched in patients with autism (Glessner et al., 2009). Recently, maternal duplications of the 15q11-q13 region encompassing *UBE3A* (Bucan et al., 2009) have been shown to confer a predisposition to ASD. Mice with increased dosage of maternally expressed Ube3a exhibit autism-related behaviors and show suppression of glutamatergic, but not GABAergic synaptic transmission further point to an important role of *UBE3A* gene dosage in neuronal function and its potential contribution to the autism traits of individuals with 154q11-q13 duplication (Smith et al., 2011). Additionally, multiple autism-linked genes, *PCDH10*, *MEF2*, *FMRP*, have recently been shown to mediate synapse elimination via proteasomal degradation of synaptic scaffolding protein PSD-95 (Tsai et al., 2012).

Mutations in another ubiquitin ligase, UBE3B, a paralog of UBE3A, have been found in patients with blepharophimosis-ptosis-intellectual disability syndrome and Kaufman oculocerebral syndrome (Basel-Vanagaite et al., 2012; Flex et al., 2013) further reinforcing the physiological importance of ubiquitination in neuronal development and function in mammals. However, the substrate specificity and biological function of UBE3B have yet to be determined. Deficiency of the XLID gene *UBE2A*, which encodes an ubiquitin-conjugating enzyme (E2) (RAD6A), has recently been shown to cause defective synaptic function as a consequence of mitochondrial failure in drosophila (Haddad et al., 2013).

Using both in vitro and in vivo ubiquitination assays, it was found that RAD6A in conjugation with an E3 ubiquitin liagase such as Parkin, ubiquitinates mitochondrial proteins to facilitate the clearance of dysfunctional mitochondria in cells (Haddad et al., 2013). The XLID protein MID1, a microtubule-associated ubiquitin E3 ligase, facilitates MID1-dependent regulation of protein phosphatase 2A (PP2A). It has recently been shown to catalyze the polyubiquitination of alpha 4 (α4), a key regulator of PP2A and mTOR (Du et al., 2013). Mutations in another E3 ubiquitn ligase, HUWE1, have been found in patients with ID (Froyen et al., 2008). It has recently found to be essential for synchronizing neuronal and glial cell differentiation in the developing cerebellum (D'Arca et al., 2010). *HUWE1*-deficient mice show profound cerebellar abnormalities (D'Arca et al., 2010).

The XLID protein CUL4B is a member of the cullin family of E3 ligase complexes that acts as scaffold proteins and recruit specific substrates for ubiquitination and subsequent degradation (Badura-Stronka et al., 2010; Tarpey et al., 2007; Zou et al., 2007). Lack of Cul4b in mice leads to embryonic lethality (Chen et al., 2012; Jiang et al., 2012). Some dendritic features, including the complexity, diameter, and spine density in the hippocampal neurons were affected by Cul4b deletion (Chen et al., 2012). CUL4B has been implicated in degradation of Cdt1 (chromatin licensing and DNA replication factor 1) and camptothecin (CPT)-induced topoisomerase I (Topo I) (Kerzendorfer et al., 2010). Patients harboring CUL4B mutations-derived cells show impaired CPT-induced Top1 degradation and increased Top1-mediated DNA breakage (Kerzendorfer et al., 2010). Recently, CUL4B is found to positively regulate CDK2-CDC6 cascade promoting DNA replication licensing (Zhou et al., 2013). Interestingly, authors found that the upregulation of CDK2 by CUL4B is through the transcription repression of miR-372/373 (Zhou et al., 2013). CUL4B has also been shown to target WDR5, a core subunit of histone H3 lysin 4 (H3K4) methyl transferase complexes for ubiquitination and degradation (Nakagawa and Xiong, 2011). CUL4B mutations are recently found to be defective in promoting TSC2 and cyclin E degradation and positively regulating mTOR signaling in neocortical neurons (Wang et al., 2013). Activation of the mTOR pathway increases dendritic complexity (Jaworski et al., 2005; Kumar et al., 2005) and has been observed in mouse models *of* Fragile X and tuberous sclerosis, two important causes of ID (Ehninger et al., 2008; Sharma et al., 2010).

Cell adhesion molecules in trans-synaptic signaling: the synaptic cleft

Cell-adhesion molecules (CAMs) play critical roles in brain development, and are crucial for the formation initial contact between pre- and postsynaptic compartments, and functional maturation and maintenance of synapses (Betancur et al., 2009; Missler et al., 2012). Neuronal CAMs provide anchors for scaffolding proteins (Missler et al., 2012; Scheiffele, 2003). The majority of CAMs at synaptic clefts are members of the cadherin family, immunoglobulin superfamilies, integrin family, as well as the neurexins and their binding partners, the neuroligins. Mutations in several of these neuronal CAMs are associated with ID and ASD or ASD susceptibility. The finding of many independent, individually rare genetic variants in synaptic CAMs such as *CDH9, CDH10, CDH15,* PTCHD1, PCDH9, PCDH10, PCDH19, CNTN4, CNTNAP2, KIRREL3, NLGN3, NLGN4X, NRXN1, SHANK2, SHANK3 implies the synaptic cell-adhesion pathways have a significant role in cognitive and behavioral function (Bakkaloglu et al., 2008; Berkel et al., 2010; Bhalla et al.,

2008; Glessner et al., 2009; Jiang et al., 2013; Morrow et al., 2008; Noor et al., 2010; O'Roak et al., 2012; Pagnamenta et al., 2011; Pinto et al., 2010; Sanders et al., 2011; Vincent et al., 2012; Wang et al., 2009). However, clinical manifestations in patients do not always correlate with the genetic mutations in synaptic CAMs. For example, in many cases identical mutations have been noted in patients as well as in apparently unaffected relatives. This would suggest the existence of a compensatory mechanism or concomitance of other unknown genetic or non-genetic factors. It is also important to note that studies suggest that synaptic adhesion molecules might have overlapping functions or act together at synaptic sites as no single pair of synaptic adhesion molecules seems to be sufficient to accomplish all aspects of synaptic development. A large number of synaptic CAMs belong to cadherin (CDH) and protocadherin (PCDH) families of proteins which primarily mediate hemophilic adhesion to support cell adhesion. A role for cadherins in neuropsychiatric disorders has recently been reviewed (Redies et al., 2012).

Other synaptic CAMS belong to the neurexin and neuroligin families of proteins. The interaction between presynaptic neurexins and postsynaptic neuroligins, which act as a Ca^{2+} dependent cell adhesion molecules in both excitatory and inhibitory synapse formation, have been studied extensively. Neurexins encode two major isoforms, α (long) and β (short), differing in their extracellular domains. Binding of neurexins to neuroligins is mediated by the sixth LNS (laminin, neurexin, sex-hormone-binding globulin) domain of α-neurexin, and the single LNS-domain of β-neurexin (Reissner et al., 2008). Both neuroligins and neuroxin exhibit synaptogenic activity in cell culture assays (Chih et al., 2005; Graf et al., 2004; Nam and Chen, 2005; Zhang et al., 2010). However, double or triple α-neurexin knockout mouse exhibits a synaptic transmission defect without any impairment in synapse formation (Dudanova et al., 2007). Similarly, mice deficient in one or more neuroligin genes show normal synapse numbers but alterations in the recruitment of postsynaptic receptors to glutamatergic, GABAergic, and glycinergic synapses (Missler et al., 2003; Varoqueaux et al., 2006). Chubykin and co workers reported that different neuroligins act on distinct types of synapses via activity-dependent mechanisms (Chubykin et al., 2007). Interestingly, the *Nlgn3* R451C knock-in mouse, which replicates the autism-linked human *NLGN3* mutation (Jamain et al., 2003), exhibited impaired social interactions, enhanced inhibitory synaptic transmission with no apparent effect on excitatory synapses (Tabuchi et al., 2007). However, these observations were not replicated in a different study with independently generated R451C knock-in mice probably due to genetic background difference (Chadman et al., 2008).

Intracellularly, the cytoplasmic tails of neurexins contain a PDZ-domain binding motif that binds to the presynaptic scaffold molecule CASK and MINT (Munc 18 interacting protein; lin-10), which couple neurexin signaling to synaptic vesicle exocytosis (see above). ID- and ASD- associated protein ProSAP2/Shank3 interacts with the cytoplasmic tail of neuroligins and recently, it was found that synaptic levels of ProSAP2/Shank3 regulate AMPA and NMDA receptor-mediated synaptic transmission and induce widespread changes in the levels of presynaptic and postsynaptic proteins via neurexin-neuroligin transsynaptic signaling (Arons et al., 2012). ASD-associated mutations in ProSAP2/Shank3 were found to disrupt postsynaptic AMPA and NMDA receptor signaling and also interfere with the ability

of ProSAP2/Shank3 to signal across the synapse to alter presynaptic structure and function (Arons et al., 2012).

Contactin associated proteins (CNTNAPs) are similar to neurexin. Although synaptic function of the ASD and ID associated CNTNAP2 is not clear, it was recently shown that while the wild-type protein localizes to the cell surface, some mutants had an altered cellular localization (Falivelli et al., 2012). A missense mutation (D1129H) showed severe trafficking abnormalities whereas a frame shift mutation that caused a form of syndromic epilepsy resulted in secreted soluble proteins suggesting that structural or signaling functions of the membrane tethered form are lost (Falivelli et al., 2012).

Therapeutic implications and challenges

As evident from the proceeding discussion, many known ID and ASD genes are involved in various physiological processes and many of these genes converge on distinct and common pathways altering neuronal functions (Delorme et al. 2013). Furthermore, an understanding of genes, pathways and associated molecular and cellular mechanisms in many cases of ID and ASD further provides a means for exploring therapeutic approaches in at least some cases of ID and ASD. Indeed, several recent studies in model systems suggest that neurological disorders, like Rett syndrome, Angelman syndrome, Kleefstra syndrome and Fragile X syndrome, are not permanent and hint at the possibility of rescuing, reversing or ameliorating neurological deficits (Chang et al. 2008; Dölen et al. 2010; Guy et al. 2007; Huang et al. 2011; Kramer et al. 2011; van Woerden et al. 2007).

However, a recent paper by Auerbach et al. (2011) highlighted at least one potential problem with the assumption that knowledge of pathways may have universal therapeutic benefits. Auerbach and co-workers showed that even though mutations in the *Tsc2* gene and the *Fmr1* gene in mice resulted in LTD, *Tsc2* mutations caused diminished protein synthesis while *Fmr1* mutations caused excessive protein synthesis. As a result, each required different treatments to arrive at the same endpoint. Therefore, extrapolating to humans, a therapy designed for ASD or ID is not likely to be helpful in all cases (already known), but in fact it might even be deleterious for some individuals. Therefore, in depth knowledge of the pathway may be necessary for each patient as therapies are developed utilizing the information gleamed from this systems approach.

Summary

As indicated at the beginning of this chapter, the group of genes associated with either intellectual disability or autism spectrum disorder are involved in many of the same molecular and biological functions. This was not unexpected since ID and ASD are comorbid in many genetic entities. There is actually a rationale for this commonality of pathophysiology. ID and ASD are disorders of neurodevelopment. Thus, their associated genes likely affect the function of other genes rather than exist unconnected to other genes. They are involved in many molecular and biological functions (signaling, translation, adhesion) which are essential for normal cell function.

The breakdown of the genes involved in ID or ASD is rather consistent regardless of how the list of genes is constructed (Figures 3 and 4). If one uses the 101 X-linked intellectual disability genes (Figures 3A, 4A) or the 705 genes associated with developmental delay prepared by the Greenwood Genetic Center (Figures 3B, 4B) or the 546 ASD/ID genes listed by SFARI (https://sfari.org/resources/sfari-gene), the percentage of genes in individual category are roughly similar and display similar distribution pattern. However, the most striking finding is that a similar analysis of all the genes in the human genome (Figures 3D, 4D) gives essentially the same breakdown per category. Therefore, the genes involved or associated with ID or ASD are, in fact, not skewed towards any particular molecular or biological process function. Rather, the composition reflects the composition of the human genome. Thus, although benefit maybe gained by focusing on certain categories to identify candidate ID and ASD genes because they may account for a large fraction of the etiology, one cannot nor should ignore all categories of molecular function and biological processes. Once a candidate ID or ASD gene provides insight into a particular pathway, invariably a screen of other genes in the pathway will uncover relevant pathological mutations contributing to a similar phenotype. Therefore, although the mechanisms involved are complex, the information of the protein interactions, pathways and function provides a means of assisting families with patients with ID and ASD. This in turn can lead to a chance for therapeutic approaches which may ameliorate the ID or ASD defect in a particular patient.

Acknowledgments

Debra Marler helped prepare the manuscript. This work was supported by a grant from the National Institute of Child Health and Human Development (R01-HD039331 to A.K.S.) and from the National Institute of Neurological Disorders and Stroke (R01-NS073854 to C.E.S.). Dedicated to the memory of Ethan Francis Schwartz, 1996-1998.

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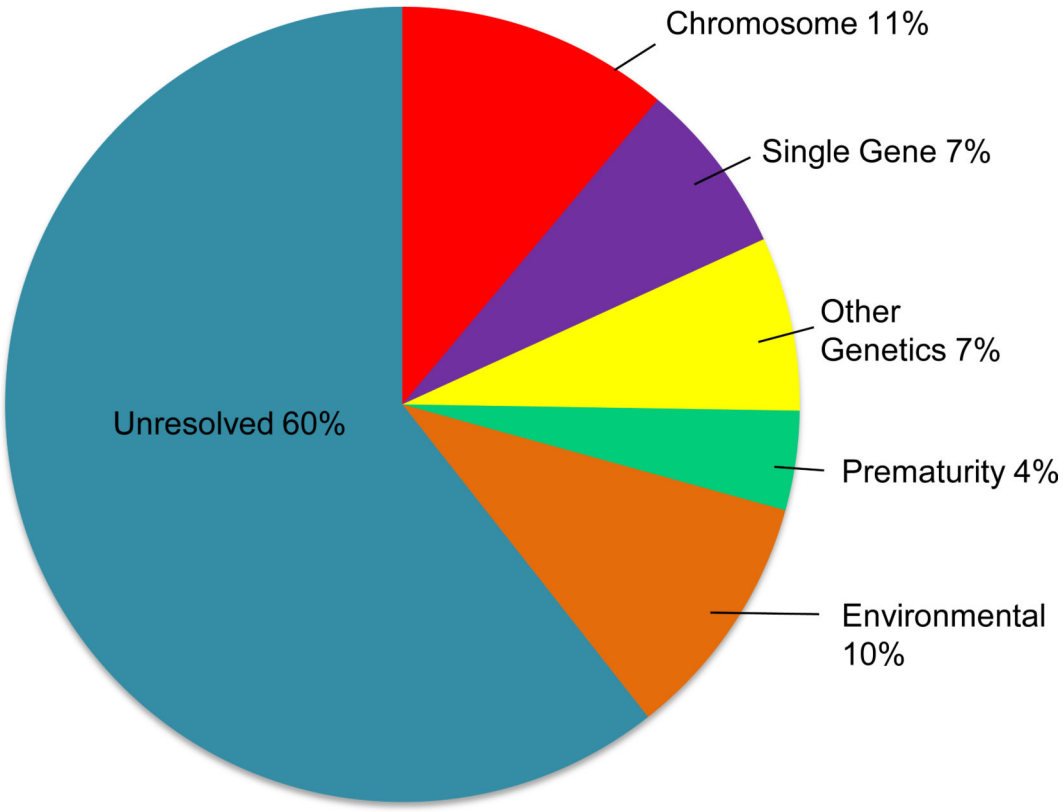

Figure 1.
Etiological causes of intellectual disability. Percentages are based on the evaluation of 15,484 individuals seen by the Greenwood Genetic Center.

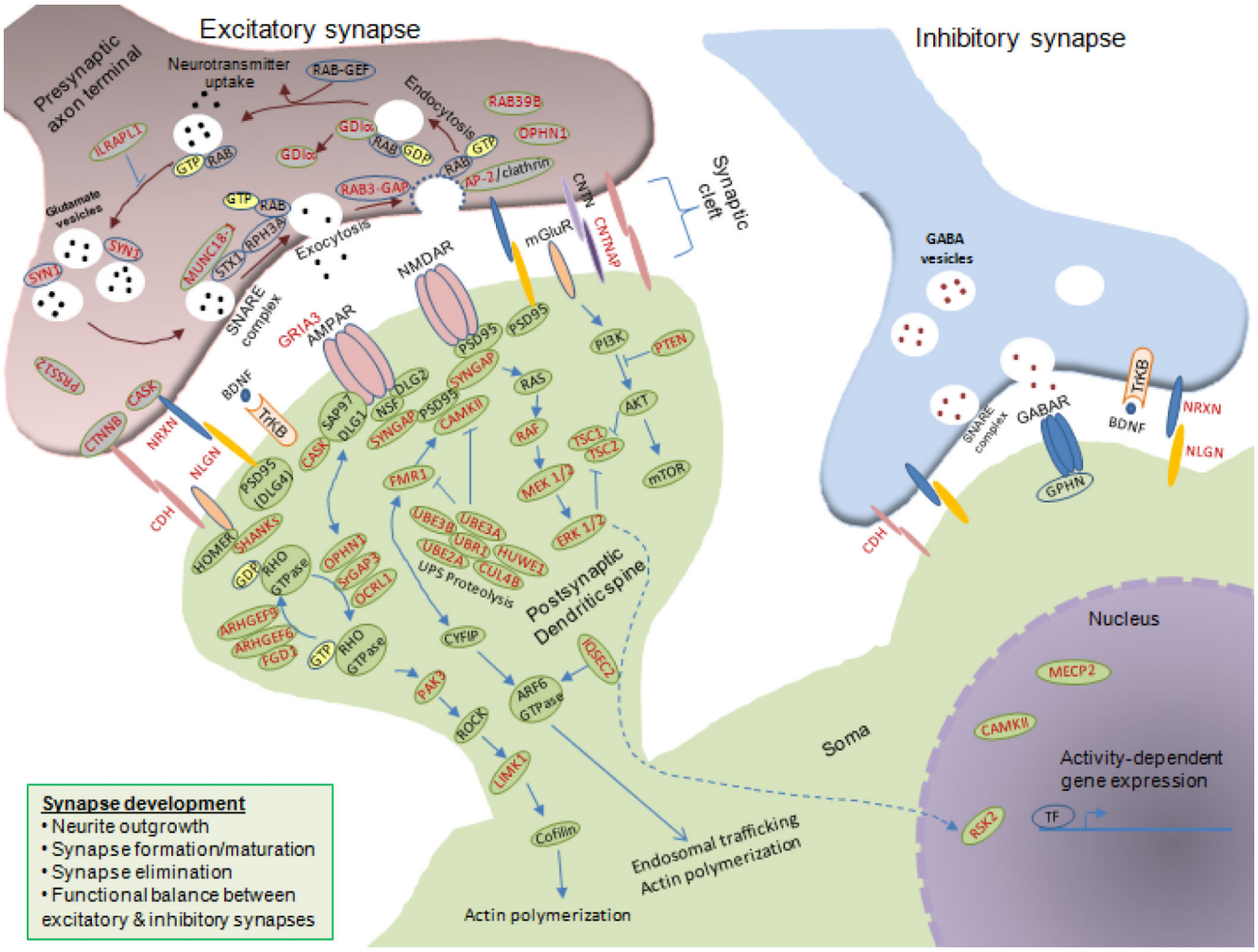

Figure 2.

Schematic diagram illustrating the complexity of the synaptic compartments and the molecular architecture of excitatory and inhibitory synapses. This figure depicts a subset of pre- and post-synaptic proteins regulating neurite outgrowth, synapse formation/maturation, synapse elimination and maintenance of a functional balance between excitatory and inhibitory synapses. The gene products implicated in neurodevelopmental disorders such as ID and ASD are shown in red type. The selected molecules and pathways shown here discussed in the text and elsewhere (Delorme et al. 2013; Ebert and Greenberg, 2013; van Bokhoven 2011; Waites and Garner, 2011).

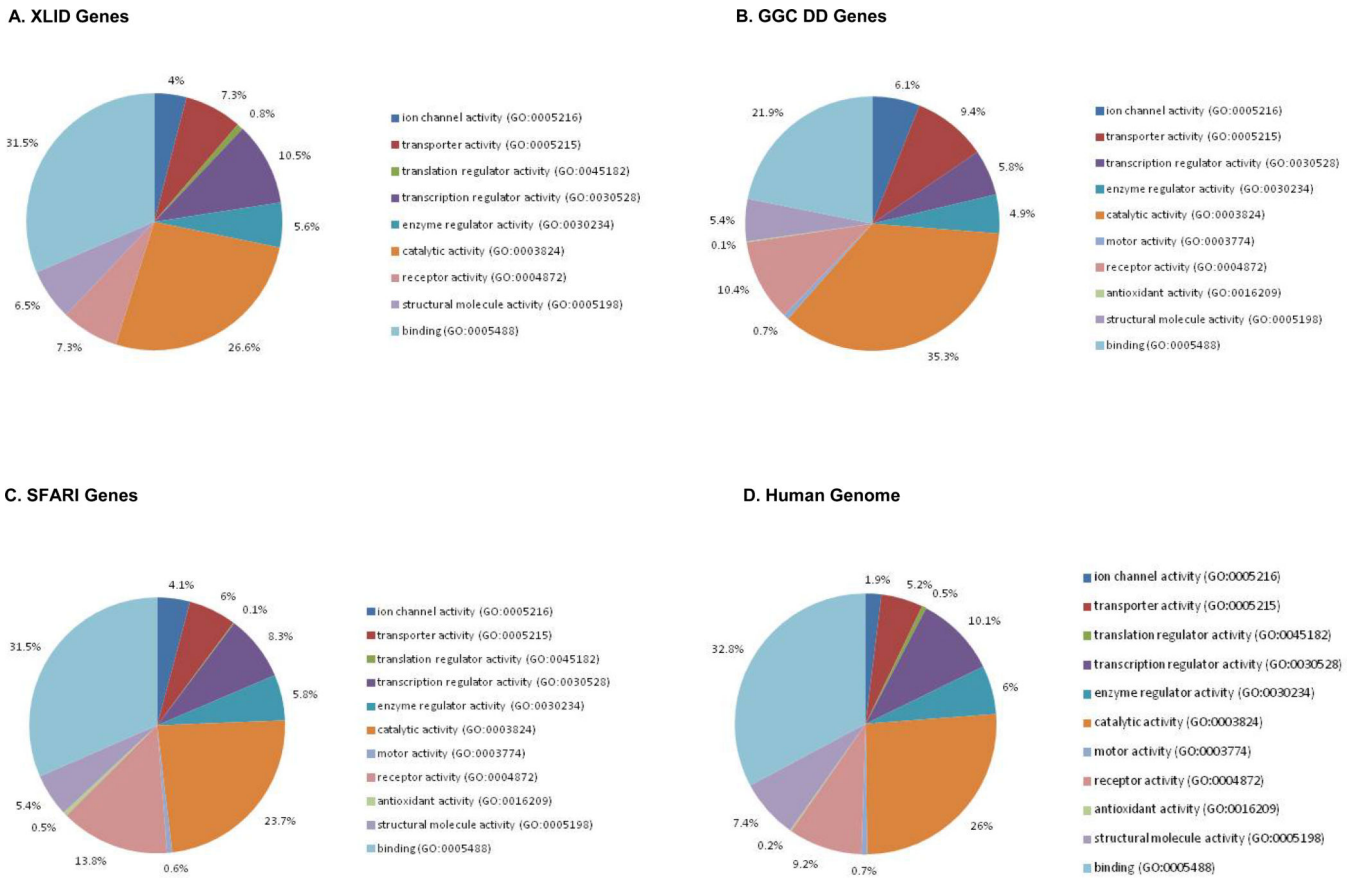

Figure 3.

Molecular function classification of genes associated with XLID, ID/ASD, developmental delay (DD), or entire human genome. Genes were classified for molecular function with Gene Ontology using the PANTHER genes classification tool (http://www.pantherdb.org/) and analyzed by the PANTHER whole genome functional analysis. GO molecular function category (Accession) and percent of genes hit against total number of Function hits are displayed as a pie chart for (A) the 101 X-linked intellectual disability (XLID) genes (total hits, 224), (B) the 705 genes associated with developmental delay prepared by the Greenwood Genetic Center (total hits, 892), (C) the 546 ASD/ID genes listed by SFARI (https://sfari.org/) (total hits, 796), and (D) the 18,331 human genes (total hits, 20,233).

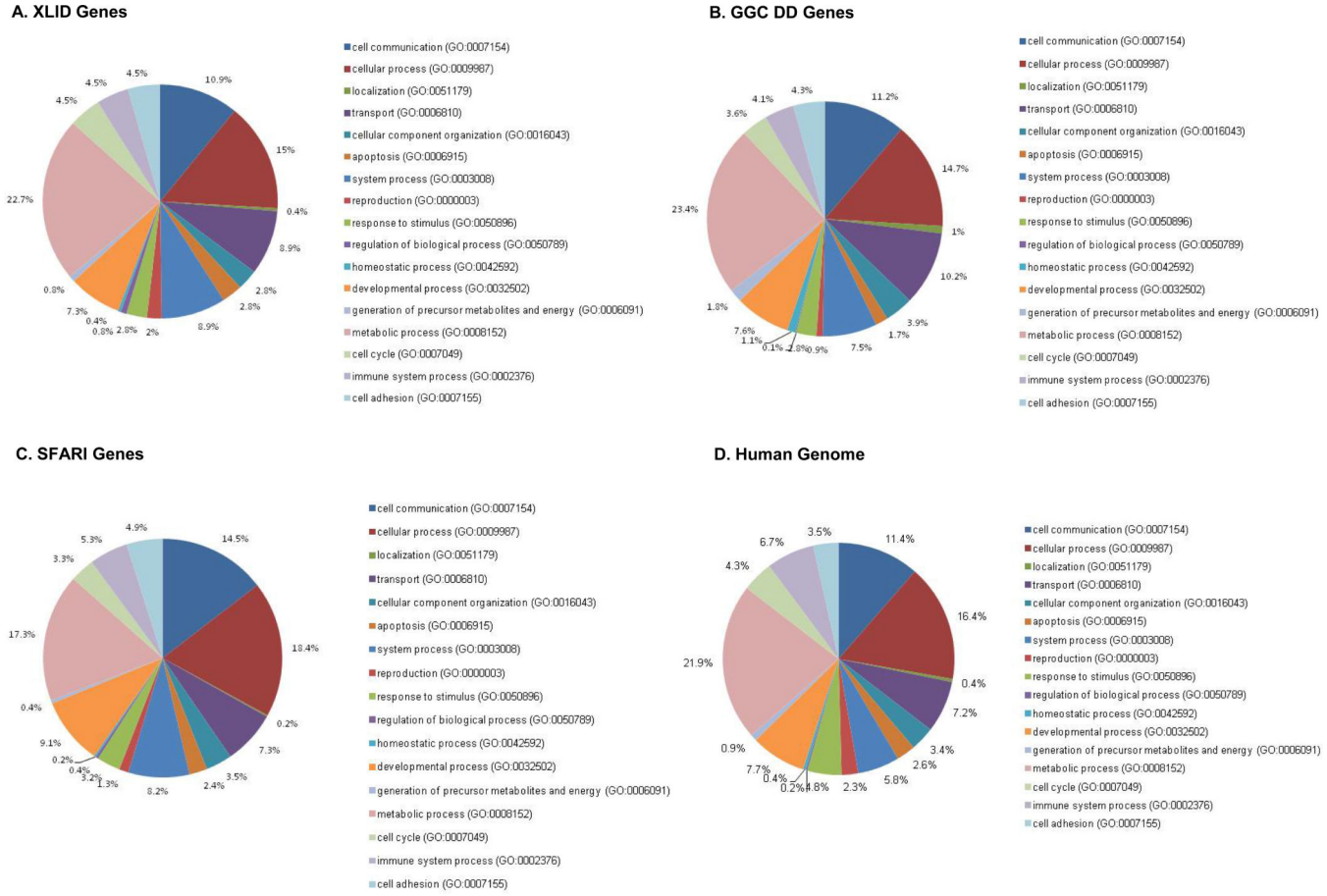

Figure 4.

Biological process classification of XLID, ID/ASD, DD genes or entire human genome. Genes were classified for biological process with Gene Ontology using the PANTHER gene classification tool and analyzed by the PANTHER whole genome functional analysis. GO biological process category (Accession) and percent of gene hit against total # Process hits are displayed as a pie chart for (A) the 101 XLID genes (total hits, 227), (B) the 705 genes associated with developmental delay prepared by the Greenwood Genetic Center (total hits, 1,651), (C) the 546 ASD/ID genes listed by SFARI (total hits, 1,638), and (D) the 18,331 human genes (total hits, 37,064).

Table 1

Selected list of ID- and ASD-associated genes regulating processes involved in neuronal morphology and communication

Biological Function	**Genes**
Presynaptic vesicle cycling and transport	*αGDI, CASK, AP-1, AP-2, AP-3, AP-4, AP4BP1, AP4E1, AP4S1, AP4M1, IL1RAPL1, OPHN1, RAB39B, STXBP1, SYN1, SYN11, SYP*
Cytoskelton dynamics	*ARHGEF6, ARHGEF9, FGD1, IQSEC2, LIMK1, OPHN1, OCRL1, MEGAP, PAK3*
Cell-adhesion and trans-synaptic signaling	*CASK, CDH9, CDH10, CDH15, CNTN4, CNTNAP2, KIRREL3, NLGN3, NLGN4X, NRXN1, PTCHD1, PCDH9, PCDH10, PCDH19, SHANK2, SHANK3*
Translational regulation, protein degradation and turnover	*CUL4B, FBXO40, FMRP, HUWE1, MID1, MEF2, PARK2, PCDH10, RFWD2, UBR1, UBE2A, UBE3A, UBE3B, UPF3B, UPF3A, SMG6, EIF4A3, RNPS1*