Review Article

Genetic Studies in Intellectual Disability and Behavioral Impairment

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Abstract

Intellectual Disability (ID, also known as mental retardation) is a debilitating neurodevelopmental disorder affecting nearly 1% of the general population worldwide. Occurrence of behavioral disorders in individuals with ID is four times higher than that in the general population. An increasing number of studies seek to find a common pathway to elucidate brain structure/function and its contribution to behavior. This article deals with different behavioral disorders reported in individuals with syndromic and non-syndromic ID and possible candidate genes, most of which are involved in synaptic formation and function. Many ID cases with behavior impairments were referred to genetic centers to identify genetic causes; therefore, the authors gathered data from their own studies along with similar published reports, to provide a review on genes involved in brain development and cognition. In this study, we argued how defects in genes with diverse functional role may contribute to behavior impairments and a brain malfunction. Evidences from individual with cognitive impairment as well as murine and drosophila animal models have been used to show behavioral consequences of functional deficits in genes speculated to play a role in cognition and learning.

Keywords: Behavioral impairment, disorder, genes, intellectual disability

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Introduction

Intellectual disability (ID), formerly known as mental retardation (MR) is a common neurodevelopmental disorder affecting nearly 1% of the general population worldwide. ID is more prevalent among children and adolescents, and it is almost two times more prevalent in low and middle income countries.[1] ID is characterized by an IQ of 70 or below, defined by significant limitations, both in intellectual functioning and in adaptive behavior, which originate before the age of 18.[2] Based on severity, ID can be classified as mild to moderate, severe, profound or unable to be classified (DSMIV).[3] Although a simplified classification is often used in studies: mild ID (IQ 50 – 70) and severe ID (IQ < 50),[4] with the majority of affected individuals belong to the mild range. A sex ratio of 1.4:1 for severe ID and 1.9:1 for mild ID suggests a significantly higher prevalence of ID in boys than in girls. Depending on various environmental factors such as the level of maternal education, as well as access to education/opportunity and health care, mild ID has a variable prevalence compared to the relatively stable prevalence of severe ID.[5] Genetic forms of ID are subdivided into two major categories: syndromic (S-ID) and non-syndromic ID (NS-ID). Syndromic ID is accompanied by the presence of other clinical, radiological, metabolic or biological features, ranging from quite well-known syndromes such as Bardet-Biedl syndrome, Smith-Lemli-Opitz syndrome, and Kabuki syndrome to rather less known or even novel syndromes.[6,7] Non-syndromic-ID is defined by the presence of ID as the sole clinical feature. However, there is a fine line between S-ID and NS-ID; neurological alterations or psychiatric disorders may be so subtle that they might easily be ignored unless they are investigated meticulously.[5,8] Dealing with excessive difficulties of a detailed investigation on human brain neurobiology, as well as ethical and practical issues has led scientists to develop genetics, pharmacological, and environmental animal models as an alternative, less challenging way to reach a better perception of pathophysiology of disorders or inventing therapeutics approaches. However it still remains challenging in some areas including the penetrance of a given genetic variant, how clearly it correlates with a specific disorder and the tricky nature of genetic manipulation. Other consideration comprises difficulties in establishing psychiatric diagnoses of humans symptoms in other living beings and the approximate correspondence of issues such as abnormal social behavior, motivation, working memory and emotions in animals compared to humans.[9]

Here we aimed to review latest and detailed analyses of behavior impairments frequently in individuals with cognitive/intellectual disabilities and animal models of some disorders. We also aimed to study the discovery of genetic causes behind these aberrant manifestations.

Behavioral disorders in children with an intellectual disability

Based on epidemiological studies, the co-occurrence of neurodevelopmental disorders seems to be more frequent than expected by chance.[10] Widely debated in the literature, the prevalence of psychopathology in subjects with ID is about four times higher than that found in the general population.[11] A high rate of behavioral disorders has been reported in people with ID, including aggression, destructiveness, self-injurious behavior (SIB), temper tantrum, hyperactivity, screaming/shouting, scattering objects around, wandering, night-time disturbance, objectionable personal habits, antisocial behavior, sexual delinquency, and attention-seeking behavior.[12] In a population-based study by Strømme and Diseth, psychiatric diagnoses were present in 42% of the population with severe ID and 33% of the population with mild ID, and the most common diagnosed disorder was hyperkinesia per-

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vasive developmental disorder.[13] In their meta-analytic study, McClintock, et al. concluded that individuals with severe/profound degree of ID are more likely to show self-injury and stereotype than individuals with mild/moderate ID. Self-injury, aggression and disruption to the environment were shown to be significantly more likely in individuals with a diagnosis of autism, whereas individuals with deficits in receptive and expressive communication were considerably more likely to show self-injury.[14] Using the Five-To-Fifteen questionnaire (FTF) in a group comprising all pupils with clinically diagnosed mild ID, Lindblad, et al. reported high rates of problems in perception (88%), language (79%), social skills/autism (76%), memory (67%), emotional problems (58%), motor skills (55%), and executive functions/attention deficit hyperactivity disorder (ADHD) (55%).[15] In their study on observed neurologic and medical disorders in children with ID in Northern India, Jauhari, et al. found a high prevalence of comorbidities which increased with the severity of ID but ADHD, autism, and violent behavior showed a decreasing rate.[16] Comparing the rates of comorbid problems and ADHD symptom levels in two groups of children with ADHD with and without mild ID (IQ score 50 – 69) revealed that children with ADHD and mild ID did not seem to differ from those without ID in terms of ADHD subtype and number of ADHD symptoms,[16] and according to Simonoff, et al. ADHD problems are likely to be more common in children with ID.[17] Di Nuovo, et al. studied comorbid pathologies in 184 individuals with ID, and concluded that comorbidity is a differentiating factor among mentally retarded subjects with an emphasis on attention, mood and anxiety disorders that impact on social functioning and well-being.[11] In 7- to 20-year-olds with ID, Dekker, et al.[18] studied three major disorders, including, anxiety disorders, mood disorders, and disruptive disorders (including ADHD, oppositional defiant disorder (ODD), and conduct disorder (CD)), and found a high rate of impairment and comorbidity. Rates of individuals with autism spectrum disorders (ASD) and ID have been estimated to be about 50% – 70% of all ASD cases.[19,20] Matson and Shoemaker (2009) provide an excellent overview on the relationship between ID and ASD,[19] according to which, among many associated challenging behaviors such as anxiety, depression, and schizophrenia, ID has the greatest overlap with those in the autism spectrum, suggesting possible genetic similarities. According to Vig and Jedrysek, the more severe the person's ID, the greater the likelihood of ASD.[21] Self-injurious behavior (SIB), a severe and chronic form of aberrant behavior, is commonly found in many disorders including Tourette's syndrome and schizophrenia. In a study by Matson, et al. regarding co-occurring behaviors, individuals with SIB were more likely to show challenging behaviors of physical aggression, property destruction, sexually inappropriate behavior and stereotypes when compared to controls.[22]

The relationship between brain and behavior

A bidirectional (mutual) relationship between brain and behavior is the central part of cognitive development. Underlying mechanisms can be examined by studying anatomical changes in the brain, based on experiences, which provide us with a more mechanistic basis for concepts such as cognitive reserve or brain maintenance.[23] Although brain changes at the cellular level cannot be easily probed, imaging of experience-dependent changes in the brain's macrostructure offers a unique window into human learning and development.[24] With many environmental and genetic factors playing a role in development of the central nervous system, it is not surprising that such heterogeneity is seen in ID cases. Emerging novel technologies such as next generation sequencing (NGS) have provided scientists with a rapid approach to identify a large group of causative genes using rising trajectories.[25] As such, is a recent large-scale (n > 1000), genotype-driven study which was conducted to discover novel genetic causes in children with severe, undiagnosed developmental disorders, with ID or developmental delay (87% of children) as most commonly observed phenotypes. By using a combination of exome sequencing, exome-focused array comparative genomic hybridization (exome-aCGH) and genome-wide genotyping on the trios, this study led to identification of 12 novel genes associated with developmental disorders and a subsequent 10% (from 28% to 31%) increase in the diagnostic yield,[26] Taken all together, over the past two decades 450 causative genes for ID have been identified. While many of those genes are accompanied by brain disorders, including neuronal heterotopias, lissencephaly and microcephaly, other genes make no observable changes to the brain structure and architecture.[27] Changes in the compartments, pre- and post-synaptically, as well as dendritic spines of the brain have been reported in a mouse model of Fragile X syndrome (FXS).[28] Several studies have focused on copy number variants association with an increased risk of neurodevelopmental disorders.[29,30] Referring to the data from the largest available studies on schizophrenia (SCZ), developmental delay (DD), autism spectrum disorders (ASD) and various congenital malformations (CM), Kirov, et al. estimated the penetrance of previously associated CNVs in a new sample comprising of 6882 cases and 6316 controls. Kirov, et al. also found that the majority of the increased risk conferred by CNVs is towards the development of an earlier-onset disorder, such as DD/ASD/CM, rather than schizophrenia.[30] Moreno-De-Luca, et al. addressed recent genetic findings from whole genome copy number variant analyses and sequencing studies. Since different disorders have some genetic causes in common, Moreno-De-Luca, et al. proposed "developmental brain dysfunction" as a conceptual framework underlying neurodevelopmental and neuropsychiatric disorders, which are typically manifested as impairments in cognitive, neuromotor, or neuro-behavioral functioning and, in some cases, observable anatomic or neurophysiological findings.[10]

Overview of behavioral disorders in well-known syndromic intellectual disabilities

Behavioral disorders have been reported on different S-ID. A study by Myers, et al. on 497 individuals with Down syndrome revealed an overall 22.1% frequency of psychiatric disorders. Younger individuals exhibit anxiety disorders, disruptive and repetitive behavior and the older subjects more often manifest major depressive disorder.[31] Ekstein, et al. reported a high prevalence of ADHD among children with Down syndrome.[32] Investigation of non-food obsessions and compulsions in 91 people with Prader-Willi syndrome (PWS) indicated an increased risk of obsessive compulsive disorder (OCD) in persons with PWS.[33] Angelman syndrome (AS), a genetic disorder characterized by abnormalities or impairments in neurological, motor and intellectual functioning, has been reported to be associated with behavioral problems. In a population-based sample, Steffenburg, et al. analyzed autistic disorder comorbidity with AS and concluded that a diagnosis of AS should be considered in all patients with the combined autistic disorder, severe ID, and epilepsy.[34] Accord-

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ing to Summers, et al. behavioral problems were present in males and females of all ages, and included language deficits, excessive laughter, hyperactivity, short attention span, problems with eating and sleeping, aggression, noncompliance, mouthing of objects, tantrums, as well as repetitive and stereotyped behavior.[35] Cognitive and language problems, social anxiety, avoidance of eye contact, and hand stereotypic movements along with some or all symptoms of autism, have been reported in individuals with Fragile X syndrome (FXS).[36] In their paper, Garber, et al. reviewed behavioral aspects and emotional characteristics in individuals with FXS which comprised autistic-like features along with impaired social skills, anxiety and mood disorders, hyperactivity and impulsivity. Females with the premutation or full mutation have also been reported to exhibit some manifestations, including social anxiety.[37] Investigation of compulsive, self-injurious, and autistic behaviors in children and adolescents with FXS revealed that autistic and compulsive behaviors are highly prevalent in FXS with lowered levels of Fragile X mental retardation protein (FMRP) and cortisol as possible markers for these behaviors.[38] However, Rogers, et al. suggest that the full syndrome of autism occurs in a minority of persons with FXS which might be more prominent earlier in life and probably occurs more often among those with more severe ID.[36] Hessl, et al. studied two candidate genes known to affect mood and aggression, the serotonin transporter (5-HTTLPR) and monoamine oxidase A (MAOA-VNTR) polymorphisms, in males with FXS. Their results showed a significant effect of 5-HTTLPR genotype on aggressive/destructive and stereotypic behavior.[39] The data implies a role for secondary genes to modify the behavioral phenotype expression, even those involving a single gene etiology such as FXS.

Aberrant social behavior, including social anxiety and impaired social cognition have been reported in a mouse model of FXS.[40] Mutation in *FGD1*, a gene reported in individuals with ID, has also been reported in the X-linked form of individuals with Aarskog–Scott syndrome (AAS). Various degrees of mental impairment and/or behavioral disorders, including hyperactivity and attention deficiency were observed, indicating that this gene may play a role in ADHD susceptibility.[41,42] Behavioral disorders have also been reported in FG syndrome (FGS) also known as Opitz–Kaveggia syndrome, an X-linked recessive form of intellectual disability (XLID). Graham, et al.[43] compared behavioral and personality characteristics between boys with FG and boys with S-ID and NS-ID including eight with Down syndrome, seven with Prader-Willi syndrome, eight with nonspecific ID, and 13 with Williams syndrome.[43] Regarding WS and PWS boys, maladaptive behaviors were significantly less observed in FG boys and made them more similar to DS boys. Compared with Williams syndrome, a significant decline in anxiety and withdrawn were seen in boys with FG, but socially oriented, and attention-seeking behaviors remained the same. While on the Reiss Profile, boys in both groups appeared to be quite similar. On the Vineland Scales, which were used in the FG sample to assess communication, daily living skills, and socialization, a significant relative strength in social skills was observed in patients. Piluso, et al. reported FG syndrome in an Italian family with a missense mutation in CASK, with affected males showing many clinical signs typical of FG syndrome, such as ID, relative macrocephaly, congenital hypotonia, severe constipation, and behavioral disturbances.[44]

Microdeletion/duplication syndromes

Chromosomal microdeletions are commonly seen among individuals with neurodevelopmental disorders or ASD, but the genetic contributors have yet to be identified. In their study, Talkowski, et al.[45] characterized a microdeletion syndrome previously described as Pseudo-Angelman syndrome or autosomal-dominant intellectual disability (ADID) type 1 (MRD1). Their large-scale study led to the identification of 65 structural rearrangements spanning the 2q23.1 region, all of which disrupted a single gene in the critical region, MBD5, a member of the methyl CpG-binding domain protein family. Followed by an extensive analysis of phenotypic features, they found that the core phenotype observed in 2q23.1 deletion syndrome, including ID and behavioral problems is similar to partial or complete deletion of *MBD5*.[45,46] Subsequent reported reciprocal deletion and duplication at 2q23.1 suggested a role for *MBD5* in ASD,[47] which is concordant with autistic-like features observed in individuals with unexplained ID for whom a whole-genome screening by array-based comparative genomic hybridization led to identification of *de novo* mutations in *MBD5*.[48] *MED12* mutation, particularly (p.R961W) has also been reported to be associated with Opitz–Kaveggia syndrome. The behavior phenotype of hyperactivity, affability, and excessive talkativeness is very frequent in individuals with MED12 mutation, along with socially oriented, attention-seeking behaviors.[49] Du Souich, et al. studied a five-generation family of Russian-Doukhobor descent with XLID and distinctive features in affected males with prominent characteristics, including mild to severe ID, cortical malformation, microcephaly, seizures, thin build with distinctive facial features and behavioral problems consisting of irritability, aggression, as well as autistic-like features. Comparison of syndromic patients with same clinical features, including Lujan–Fryns syndrome (LFS), Snyder–Robinson syndrome (SRS), and zinc finger DHHC domain-containing protein 9-associated ID exhibited many similarities. The differences, though distinguish this as a previously undescribed syndrome with the subsequent linkage analysis revealing a 5 Mb region on Xq28 segregating with the disease.[50] Brunetti-Pierri, et al. described 21 probands with 1q21.1 microdeletion and 15 probands with 1q21.1 microduplication. Along with developmental delay and/or learning disabilities being reported in most cases, behavioral abnormalities were frequently observed, including ADHD, autism, anxiety/depression, antisocial behavior, aggression, and even hallucinations.[51] As they are associated with autism and developmental delay (DD), as well as their common occurrence, 16p11.2 chromosomal rearrangements have been the center of attention in many studies. In a search for detailed phenotypic manifestations of individuals with 16p11.2 imbalances, Shinawi, et al. investigated 27 individuals with 16p11.2 rearrangements. Behavioral problems were found in nearly 40% of subjects; a higher rate of ADHD was seen in patients with duplication and autism were present in patients with deletion.[52] Using array-comparative genomic hybridization (CGH) analysis, Nizon, et al. reported 17 new patients with Xp11.23p11.22 microduplication. Patients shared several common major characteristics, including moderate to severe ID, early onset of puberty, language impairment, and age related epileptic syndromes such as West syndrome and focal epilepsy with activation during sleep evolving in some patients to continuous spikes-and-waves during slow sleep. Behavioral disorders including, aggressive behavior, attention deficit, and hyperactivity were noted in some patients, suggesting possible candidate genes: *FTSJ1* and *SHROOM4* for ID along with *PQBP1* and *SLC35A2* for epilepsy.[53] Changes in

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Coffin–Lowry syndrome (CLS) gene, *RPS6KA3*, which was previously shown to be associated with reduced control of exploratory behavior in mice lacking the gene,[54] has been proposed to be involved in some behavioral manifestations in individuals with ID. Using array-CGH analysis, Matsumoto, et al. detected a 584-kb microduplication spanning 19.92 – 20.50 Mb of Xp22.12 (including *RPS6KA3*) in a family with two members. One member had mild ID and localization-related epilepsy, whereas the other one presented borderline IQ and ADHD.[55] *IQSEC2* gene, located on chromosome Xp11.22 and known for the maintenance and homeostasis of the brain, has been proposed to play a significant role in the development of XLID with seizures.[56] Fieremans, et al. reported on a girl carrying a *de novo* 0.4 Mb deletion containing six coding genes, including *KDM5C* and *IQSEC2*. The girl carrying a *de novo* 0.4 Mb deletion, had severe ID and autistic features suggesting that heterozygous loss-of-function in *KDM5C* and/or *IQSEC2* genes might contribute to severe ID in female patients.[57]

ARX gene mutations come with a broad spectrum of phenotypes, including nonsyndromic X-linked intellectual disability (NS-XLID), infantile spasms, seizures, and autism.[58,59] In 2002, two families with the same mutation (a 24-bp duplication (428 – 451 dup (24bp)) in *ARX* gene were reported in which one individual had autism and two were manifesting autistic behavior.[58] Szczaluba, et al. conducted a study on genotype–phenotype associations for *ARX* gene duplication in 18 individuals with XLID; although manifestations were diverse, and no behavioral disorder was reported.[60] In another study, screening the *ARX* gene in 226 male patients with autism spectrum disorders and ID by direct sequencing of all exons and flanking regions indicated that mutations in the *ARX* gene are very rare in autism.[61] These contradictory results necessitate more studies to define the *ARX* contribution to behavioral disorders along with ID. Table 1, provides an overview of above-mentioned genes.

Functional contribution of genes in behavior shaping

A variety of genes with diverse cellular roles contributing to cognitive impairment and behavior disorders have been recognized. See: "Genetics of Recessive Cognitive Disorders (Kahrizi, et al. 2015)" for common molecular functions contributing to ARID.[62] There are so many genes involved in learning and those that are deficient in neuropsychiatric disorders. Here, genes in which defects have been reported to be accompanied by behavior impairments are categorized into five main groups and are as follows:

Synaptic proteins

Communication in the brain is performed at intriguingly adaptable structures called synapses, which make neuronal cells capable of establishing a connection and transmitting the message. Genetics plays a major role in the growth and plasticity of neuronal circuitry, but the structure, size, shape, number, and pattern of synaptic connections are ultimately determined by experience. As they are involved in many neuropsychiatric disorders, alterations in synaptic structure and function have been the subject of research in many disorders such as autism, ID, schizophrenia and Huntington's disease (HD).[63–69] At the cellular level, protrusions from a neuron's dendrite, called dendritic spines, receive input from a single synapse of an axon, and the subsequent processing leads to transmission of an electrical signal to the neuron's cell body. Studies have shown a higher spine density in ASDs,[70] and dendritic aberrations, as well as miscommunication between neurons have been proposed to be involved in the pathogenicity of a broad spectrum of neuropsychiatric diseases including ID, anxiety, schizophrenia and autism, implying that defects in neuronal network formation or in properties of brain plasticity likely contribute to cognitive impairment.[71–74] Kulkarni and Firestein provide a review which discusses the morphology, cytoskeletal structure, and architecture of dendrite development, branching and their altered functional capabilities altered in various brain disorders.[73] To elucidate consequences of dendritic structure de-

Table 1. Genes responsible for syndromic intellectual disabilities

Gene	Function (www.omim.org)	Inheritance	Phenotype
ARX (MIM 300382)	Aristaless-related homeobox protein, playing crucial roles in cerebral development and patterning	XL	ID + Autism
CASK (MIM 300172)	A calcium/calmodulin-dependent serine protein kinase that is a member of the membrane-associated guanylate kinase (MAGUK) protein family.	XL	ID, Hyperactivity, aggression
FGD1 (MIM 300546)	A guanine-nucleotide exchange factor (GEF), binds specifically to the Rho gtpase CDC42	XL	Hyperactivity and attention deficit
IQSEC2 (MIM 300522)	A guanine nucleotide exchange factor for the ARF family of GTP-binding proteins	XL	ID + Autism
MBD5 (MIM 611472)	A member of the methyl cpg-binding domain protein family	AD *(de novo)*	ID, Autism, Stereotypic repetitive behavior
MED12 (MIM 300188)	Mediator of RNA polymerase II transcription, subunit 12; can function in transcriptional activation or repression depending on the factors with which it interacts	XL	ID, Hyperactivity, Maladaptive Behavior, Aggression, Anxiety, Inattention
RPS6KA3 (MIM 300075)	A member of the RSK (ribosomal S6 kinase) family of growth factor-regulated serine/threonine kinases, known as p90 (rsk)	XL	ID + ADHD
SLC6A4 (MIM 182138)	Serotonin transporter, contains a polymorphic region (5-HTTLPR)	AR	In male with FXS: the most aggressive and destructive behavior in patients with high-transcribing long (L/L) genotype

XL: X-linked; AD: autosomal dominant; AR: autosomal recessive; ID: intellectual disability; ADHD: attention deficit hyperactivity disorder.

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fects for neuronal function and behavioral performance, Ryglewski, et al. selectively removed dendrites from a subset of identified wing muscle motor neurons. Significant dendritic defects with preserved normal axonal structure and membrane current maintained the vast majority of basic motor functions. Their result provided an evidence that deficits in performance relates to the degree of defect in the structure of dendrites; a phenomenon which according to the authors, is consistent with the observed gradual increase in ID during ongoing structural deficiencies seen in progressive neurological disorders.[75] Synaptic pathways involve neurexins (NRXN) and their postsynaptic binding partners neuroligins (NLGN) (Table 2). SHANK are the best-characterized pathways known to be implicated in ASD. Truncating mutations in *NRXN2* and *NRXN1*, as well as loss-of-function variants in *NLGN3*, *NLGN4*, *NRXN1*, and *SHANK3* are associated with autism.[68] In mice, *NLGN3* and *NLGN4* null mutations have been found to cause autism-like traits in some studies.[76] The X-linked neuroligins *NLGN3* and *NLGN4* are key elements for neuronal synapses to form and function properly; these adhesion molecules were the first synaptic genes known to be associated with autism and Asperger's syndrome.[77] A 2-base-pair deletion in the Neuroligin 4 gene (*NLGN4*), leading to a premature stop codon, was found in a large French family affected by nonspecific XLID, with or without autism, suggesting that the *NLGN4* gene is involved in autism and ID, indicating a possible common genetic origin between some types of autistic disorder and ID.[78]

SHANK3, the scaffolding protein of the postsynaptic density (PSD) of excitatory glutamatergic synapses, which binds to NLGN, is known to regulate the structural organization of dendritic spines. All three members of the SHANK gene family (*SHANK1*, *SHANK2*, and *SHANK3*) have been shown to be involved in ASD with or without ID.[79–82] Modeling of SHANK mutations in mice has shown that subtle differences in mutations within a given ASD risk gene can produce overlapping but non-identical cellular, synaptic, and behavioral phenotypes.[83] Involvement of SHANK genes in neuropsychiatric disorders such as ASD, schizophrenia, and bipolar disorder has been extensively reviewed by Guilmatre, et al. In their review Guilmatre, et al. discuss the *SHANK2* mutations/deletions/translocations in patients with ASD and mild to moderate ID, and how *SHANK3* mutations cause diverse clinical trajectories (ID only, ASD, ADHD, schizophrenia, and bipolar disorder).[84]

Membrane-associated guanylate kinases (MAGUKs) are a superfamily of scaffolding proteins, and mutations in one of its subfamilies. MAGUKs comprise synapse-associated protein *(SAP)102*, *SAP97*, *PSD93*, and *PSD95*, which are orthologs of Drosophila DLG and have been shown to be implicated in some psychiatric disorders.[85] *SAP97 (DLG1)* is located on 3q29, a region reported to be associated with ID, autism, and schizophrenia.[86–88] Mutations in *SAP102 (DLG3)* have also been reported in NS-XLID[89] and ASD.[90] *Dlg4* gene disruption in mice produced a complex range of behavioral and molecular abnormalities relevant to autism spectrum disorders and Williams's syndrome. A study has provided an initial link between human *DLG4* gene variation and key neural endophenotypes of Williams syndrome, as well as cortico-amygdala regulation of emotional and social processes more generally.[91]

Glutamatergic synapses

As the main adaptation center, the brain has a central role in stress perception and response. In animal models, remodeling of brain architecture such as dendritic atrophy and loss of dendritic spines in response to stress, was evident in neuronal populations.[92] Glucocorticoid release induced by stress, subsequently changes glutamate neurotransmission, which in turn interferes with some aspects of cognitive processing.[93] Glutamatergic synapses and genes involved in glutamate signaling have been shown to play an important role in the common pathways of neurodevelopmental disorders such as autism spectrum disorders, bipolar disorder, and schizophrenia (Table 3).[94–98] As the main excitatory neurotransmit-

Table 2. Genes encoding synaptic proteins

Gene	Function (www.omim.org)	Inheritance	Phenotype
NLGN4 (MIM 300427)	Bound to neurexins and localized to dendritic spines when overexpressed	XL	ID, Autism
PSD-95(Dlg4) (MIM 602887)	Belongs to the discs large (DLG) subfamily of the membrane-associated guanylate kinase (MAGUK) family, interacting with both N-methyl-D-aspartate (NMDA) receptors and shaker-type potassium channels and plays an important role in the formation and maintenance of synaptic junctions	AR	ID, ASD, Williams' syndrome (in mice)
SAP-97 (DLG1) (MIM 601014)	A mammalian MAGUK-family member protein that is similar to the Drosophila protein Dlg1, involved in the trafficking of ionotropic receptors	AD	ID, Autism, Schizophrenia
SAP102 (DLG3) (MIM 300189)	Synapse-associated protein 102 (SAP102), a member of the membrane-associated guanylate kinase (MAGUK) protein family	XL	ID, ASD
SHANK2 (MIM 603290)	A member of the Shank family of synaptic proteins that may function as molecular scaffolds in the postsynaptic density (PSD)	AD *(de novo)* (inherited)	ID, ASD
SHANK3 (MIM 606230)	The scaffolding protein of the postsynaptic density (PSD) of excitatory glutamatergic synapses, which binds to the NLGN	AD	ID + Autism, Schizophrenia, ADHD, Bipolar disorder

ASD: autism spectrum disorders.

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Table 3. Genes encoding proteins involved in glutamatergic synapses

Gene	Function (www.omim.org)	Inheritance	Phenotype
CACNG2 (MIM 602911)	A brain-specific transmembrane AMPA receptor regulatory protein that modulates the trafficking and ion channel kinetics of glutamate AMPA receptors. It is also a putative subunit of neuronal voltage-gated calcium channels	AD (*de novo*)	ID + Schizophrenia, Bipolar disorder
GRIA3 (MIM 305915)	Glutamate receptor 3, belongs to a family of AMPA receptors	XL	ID + Behavioral disorders
GRIK2 (GLUR6) (MIM 138244)	A subunit of a kainate glutamate receptor	AR	ID, Obsessive-Compulsive Disorder, susceptibility to ASDs
GRIN1 (MIM 138249)	Glutamate [NMDA] receptor subunit zeta-1	AD (*de novo*)	ID + Schizophrenia
GRIN2A (MIM 138253)	Glutamate [NMDA] receptor subunit epsilon-1	AD (*de novo*)	ID, Schizophrenia , ASD
GRIN2B (MIM 138252)	Glutamate [NMDA] receptor subunit epsilon-2	AD (*de novo*)	ID, Schizophrenia , ASD

ter in the brain, most synapses in the central nervous system use L-glutamate as a neurotransmitter.[99] Glutamate receptors are divided into those which open up to glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA receptors, N-methyl-D-aspartate (NMDA) receptors, and Kainate receptors (KARs), as well as those which indirectly activate ion channels through a signaling cascade involving G-protein (mGluRs).[100,101] Glutamate receptor channels (GRCs) are involved in learning, memory, and synaptic plasticity and have been proposed as a candidate gene in neurodegenerative diseases such as ID.[96] Pathogenic mutations in genes encoding for glutamate receptors, including *GRIA3*, *GRIK2*, *GRIN2A*, and *GRIN2B* have previously been shown to be associated with ID cases along with behavioral disorders.[102] As the first proof that the ionotropic glutamate receptor 6 gene (*GRIK2*, also called "*GLUR6*") is indispensable for higher brain functions in humans, a defect in the *GRIK2* gene was reported in a large, consanguineous Iranian family with ARID.[103] An association between polymorphisms in *GRIK2* gene and obsessive-compulsive disorder was later reported in a family-based study,[104] and in the first demonstration of a genome-wide significant association of common variants with susceptibility to ASDs, *GRIK2* are among the genes which show evidence of the association.[105] By sequencing seven genes encoding for NMDA receptor subunits (NMDARs) in a large cohort of individuals affected with schizophrenia or ASD, Tarabeux, et al. identified two *de novo* mutations in patients with sporadic schizophrenia in GRIN2A and one *de novo* mutation in GRIN2B in a patient with ASD. These data support the hypothesis that rare de novo mutations in *GRIN2A* or *GRIN2B* can be associated with cases of sporadic schizophrenia or ASD.[106] To elucidate the underlying cause of NSID and *de novo* mutations in synaptic genes as an important contributor, Hamdan, et al. conducted a study which showed the importance of the glutamate receptor complexes in NS-ID.[96] Hamdan, et al. sequenced 197 genes encoding glutamate receptors and their known interacting proteins in sporadic cases of NSID.They found pathogenic *de novo* truncating and/or splicing mutations in *SYNGAP1*, *STXBP1*, and *SHANK3*, along with *de novo* missense mutations in *KIF1A*, *EPB41L1*, and *GRIN1*, the gene with some reported polymorphisms associated with schizophrenia,[107–109] and *CACNG2*, a gene previously identified to be one of the aberrant loci in bipolar disorder and schizophrenia.[110]

Membrane associated proteins

Spine morphology and AMPAR-mediated synaptic transmission are critically dependent on Ankyrin-G, which accumulates by neuronal activity. The subsequent regulation of NMDA receptor-dependent plasticity has made Ankyrin-G a psychiatric risk molecule in glutamatergic synapses[111] and it has been reported in several neuropsychiatric disorders such as bipolar disorder, schizophrenia and autism (Table 4).[112] Iqbal, et al. reported on two separate cases, one with borderline intelligence, severe ADHD, autism and sleeping problems in whom disruption of the gene led to the absence of all three isoforms, whereas the other case had moderate ID, an ADHD-like phenotype and behavioral problems due to homozygous truncating frameshift mutation in the longest isoform of the same gene.[113] The gene involvement in cognitive function was further supported by a short-term memory defect in Drosophila, an animal model of the disease. Disruption at or deletion in *PTCHD1* (patched-related) gene, the transmembrane protein involved in the sonic hedgehog pathway, has been studied in individuals with ID or ASD. From systematic screening of *PTCHD1* and its 5′ flanking regions in seven families with ASD and three families with ID, Noor, et al. suggested an estimate of nearly 1% involvement of this locus in individuals with ASD or ID.[114] Filges, et al. also reported on a family with two affected boys harboring a deletion in Xp22.11, which exclusively contains the *PTCHD1* gene suggesting a possible role of this gene in XLID and autism disorders.[115] In a study on four individuals with ASD, the possible involvement of *DPYD* gene, which is the initial and rate-limiting enzyme in catabolism of pyrimidine bases, was found to have an additional missense mutation in the X-linked *PTCHD1*.[116] In a recent study by Torrico, et al. the contribution of common and rare variants of the *PTCHD1* gene to ASD and ID has been investigated.[117] A single nucleotide polymorphism (SNP) (rs7052177) predicted to be located in a transcription factor binding site, showed a significant association along with findings that showed rare missense *PTCHD1* variants only identified in the ID sample. Three ASD patients were found to have duplication

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Table 4. Genes encoding membrane associated proteins

Gene	Function (www.omim.org)	Inheritance	Phenotype
ANK3/ankyrin-G (MIM 600465)	A member of the ankyrin family of proteins that link the integral membrane proteins to the underlying spectrin-actin cytoskeleton	AR	ID + Autism, Schizophrenia, Bipolar disorder, ADHD
PTCHD1 (MIM 300828)	The trans-membrane protein involved in the sonic hedgehog pathway	XL	ID + Autism
SLC6A8 (MIM 300036)	Creatine transporter	XL	ID, Autism
SLC6A17 (MIM 610299)	A synaptic vesicular transporter of neutral amino acids and glutamate, which makes it an important role player in the regulation of glutamatergic synapses	AR	ID + Aggression, mood instability, and poor impulse control
TUSC3 (MIM 601385)	A member of the plasma membrane Mg2+ transport system	AR	Motor instability, high tendency to irritability and distraibility, anxiety traits, and an oppositional-defiant disorder

(27 bp) in the promoter region. Together, these findings support the involvement of *PTCHD1* in ASD, suggesting that both common and rare variants contribute to the disorder.[117]

A mutation in *TUSC3*, a gene formerly identified in individuals with nonsyndromic autosomal recessive intellectual disability (NS-ARID),[118–120] has recently been reported in a boy harboring a homozygous deletion with S-ID and behavioral disorders, including motor instability, a high tendency to irritability and distractibility, anxiety traits, as well as an oppositional-defiant disorder. As a member of the plasma membrane Mg^{2+} transport system, with a possible involvement in learning abilities, working memory and short- and long-term memory, authors argued that the gene could be more commonly involved in ID etiology than expected.[121] Inborn errors of creatine metabolism have been described with autism symptoms, accompanied by ID and seizures.[82] Creatine transporter defect may also be manifested as ID, language delay, seizures, and autistic behavior.[122] Creatine transporter deficiency, due to mutations in X-linked *SLC6A8* gene, has been associated with ID and autism. Hahn, et al. reported a family with XLID with speech and behavioral abnormalities, and seizures, with heterozygous female relatives also exhibit mild ID, behavioral and learning problems.[123] A year later, Rosenberg, et al. studied the prevalence of *SLC6A8* mutations in a panel of 290 patients with NS-XLID, and concluded that creatine-deficiency disorders should be considered and tested in male patients with ID, autistic behavior, epilepsy, and/or expressive speech and language delay, proposing measurements such as screening and functional tests.[124] Biochemical and clinical aspects of creatine deficiency syndromes are the subject of a review by Nasrallah, et al. who proposed that creatine deficiency syndromes could be considered in all children affected by unexplained ID, seizures, and speech delay.[125] With a combination of exome sequencing and homozygosity mapping, Iqbal, et al. revealed homozygous *SLC6A17* mutations in families from Iran and Netherlands, with affected individuals exhibiting moderate to severe ID accompanied by other phenotypes such as progressive tremor, speech impairment, and behavioral problems.[126] *SLC6A17* is predominantly expressed in the brain, encodes a synaptic vesicular transporter of neutral amino acids and glutamate, and plays an important role in the regulation of glutamatergic synapses. Further investigation elucidate the functional consequences of the mutation on mouse primary hippocampal neuronal cells and revealed the loss of dendritic spines in the mutation p.Gly162Arg.[126]

Signaling pathways

Discovery of XLID genes that are all linked to Rho GTPase signaling p21-activated kinase (PAK3), oligophrenin 1 (OPHN1), and Rho guanine nucleotide exchange factor 6 (ARHGEF6) suggests that formation of neuronal processes and synaptic plasticity are critical for cognitive functions (Table 5).[69,127] Oligophrenin-1 is a negative regulator of RhoA, which also interacts with the postsynaptic adaptor protein Homer.[128] Loss of XLID protein oligophrenin-1 has been shown to be involved in dendritic spine morphogenesis.[129] A mouse model of ophn1 deficiency generated by Khelfaoui, et al. exhibited behavioral defects in spatial memory together with impairment in social behavior, lateralization, and hyperactivity.[130] *ARHGEF9* encodes collybistin, a brain-specific guanine nucleotide exchange factor (GEF), which is essential for the gephyrin-dependent clustering of a specific set of gamma-aminobutyric acid receptors at inhibitory postsynaptic sites and also known for being involved in alteration of cell signaling transduction pathways.[131] Deletion or disruption in this gene has been shown to be implicated in individuals with ID, epilepsy and behavioral disorders.[132,133] Interleukin-1 receptor accessory protein-like 1 (IL1RAPL1), which is involved in formation and stabilization of glutamatergic synapses through the RhoA signaling pathway,[134] has also been shown to be associated with ID and ASD.[135,136] However, this result is in contradiction to a study by Allen-Brady, et al. in which they could not find any evidence for IL1RAPL1 involvement in 14 males, each representing one case from selected high-risk autism pedigrees.[137] Nawara, et al. reported a novel mutation of this gene in a family with some affected individuals exhibiting hyperactivity, autoaggressive behavior, anxiety, and stereotypic movements.[136] Franek, et al. identified two families with cognitive impairment, as well as mild dysmorphism. Behavioral disorders in affected males were impulsive and oppositional behavior, infantile autism and pervasive developmental disorder with atypical autistic behavior.[138] IL1RAPL2, another member of the interleukin 1 receptor family, is an autism candidate gene.[139] IL1RAPL2 is located in the region, which was reportedly deleted

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Table 5. Genes encoding proteins involved in signaling pathways

Gene	Function (www.omim.org)	Inheritance	Phenotype
ARHGEF9 (MIM 300429)	Rho guanine nucleotide exchange factor 6	XL	ID, Behavior disorders
DYRK1A (MIM 600855)	A member of the dual-specificity tyrosine phosphorylation-regulated kinase (DYRK) family	AD (*de novo*)	ID + Autism
GDI1 (MIM 300104)	GDP dissociation inhibitor-1 gene (*GDI1*) regulates the GDP-GTP exchange reaction of members of the rab family, small GTP-binding proteins of the ras superfamily	XL	*Gdi1*-deficient mice: defect in short-term memory, lowered aggression and altered social behavior.
IL1RAPL1 (MIM 300206)	A member of the interleukin-1 receptor family and is similar to the interleukin-1 accessory proteins, most closely related to interleukin-1 receptor accessory protein-like 2 (IL1RAPL2)	XL	ID, ASD, impulsive and oppositional behavior, infantile autism and pervasive developmental disorder with atypical autistic behavior
IL1RAPL2 (MIM 300277)	A member of the interleukin 1 receptor family	XL	ID + Autism, poor eye contact and sleep disturbance
OPHN1 (MIM 300127)	A Rho gtpase-activating protein	XL	Behavioral defects in spatial memory, impairment in social behavior, lateralization, and hyperactivity (in mouse model)
RAB39B (MIM 300774)	Mall GTPases involved in the regulation of vesicular trafficking between membrane compartments	XL	ID, Autism

in five females, three of which had strikingly similar behavioral problems, including poor eye contact and sleep disturbance.[140]

GDI1 is an identified ID gene, which encodes one of the proteins controlling the activity of the small GTPases of the Rab family in vesicle fusion and intracellular trafficking. In a study, Gdi1-deficient mice exhibited a defect in short-term memory as well as lowered aggression and altered social behavior.[141] RAB39B is a novel RAB GTPase and a neuronal-specific protein, which has been shown to be responsible for XLID associated with autism, epilepsy, and macrocephaly. Down regulation of RAB39B leads to an alteration in neuronal development and function, emphasizing the vital role of vesicular trafficking in the development of neurons and intellectual capabilities in human.[142] The dual-specificity tyrosine phosphorylation-regulated kinase 1A (*DYRK1A*) gene is located in the Down syndrome (DS)-critical region of chromosome 21 and expressed in several structures of the adult CNS. Due to these characteristics, *DYRK1A* has been studied for its possible role in human cognition[143] and brain developmental abnormalities.[144] Multiplex targeted sequencing has identified this gene as one of recurrently mutated genes, reportedly contributing to 1% of sporadic ASD.[145] A Genome-Wide Association Study (GWAS) by Tielbeek, et al. showed the strongest association (*P*-value = 8.7×10^{-5}) of *DYRK1A* with adult antisocial behavior.[146] In two unrelated patients with mutations in the gene, Ruauda, et al. reported one patient with autistic behavior[147] and Van Bon, et al. recently reported disruptive *de novo* mutations of *DYRK1A* leading to a syndromic form of autism and ID, which is in line with murine and Drosophila knockout models.[148]

Transcription regulators

De novo mutations in *DEAF1* have been shown in four individuals with severe ID and severely affected speech development, and three of them showed major behavioral problems. *DEAF1* encodes a transcription factor, which is highly expressed in the CNS, particularly during early embryonic development. A conditional knockout of *DEAF1* in the mouse brain also led to memory deficits and increased anxiety-like behavior, suggesting a role for DEAF1 in causing ID and behavioral problems, most likely as a result of impaired transcriptional regulation by *DEAF1* (Table 6).[149]

By systematic sequencing of 737 genes on the human X chromosome in 250 families with XLID, Tarpey, et al. identified mutations in *UPF3* in families with S-ID and NS-ID.[150] *UPF3B* gene is proposed to be a crucial regulator of multiple processes in brain development and has been shown to be implicated in ID, autism, ADHD and childhood onset schizophrenia.[151,152] *UPF3* is a member of the nonsense-mediated mRNA decay complex and plays a critical role in normal brain development and function, and any genetic or therapeutic intervention is predicted to result in a spectrum of neurocognitive phenotypes.[151] Upf3b-null mice have been shown to exhibit behavioral and neuropathological defects, including a specific defect in sensorimotor gating, and a commonly displayed feature in schizophrenia patients. Decreased dendritic spine density and mature dendritic spines in pyramidal cells, which are also present in schizophrenic and autistic patients, were observed by examination of the frontal cortex. Further studies on these mice showed dysregulation of several mRNAs transcribed from genes mutated in patients with ID, suggesting that nonsense-mediated RNA decay (NMD) directly interferes with regulation of many of these transcripts.[153] *KDM5C*, a gene encoding a member of an ARID protein family, acts as a histone H3 lysine 4 demethylase, suggesting a putative role in epigenetic regulation during development, cell growth and differentiation.[154] Kdm5c levels are severely reduced in differentiating GABAergic neurons and are essential for neuronal survival during zebra fish development. *KDM5A* is linked to rare monogenic forms of neurodevelopmental disease, including ID and autism.[155–158] Various studies have reported ID accompanied by different behavioral disorders in individuals harboring a mutation in *KDM5C* gene. Besides ID as a shared feature, aggressive or violent behavior was commonly seen in all patients.[158]

Proteins involved in metabolic processes

Reuter, et al. studied two unrelated families with patients exhibiting ID and some behavioral disorders who had a homozygous missense mutation in *NDST1* which is involved in heparan sulfate biosynthesis.[159] Pathogenic variants in this gene had previously been proposed to be the cause of ARID in two other families.[25] Taking four families together revealed that most of the affected in-

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Table 6. Genes encoding transcription regulators

Gene	Function (www.omim.org)	Inheritance	Phenotype
DEAF1 (MIM 602635)	A transcription factor which is highly expressed in the CNS	AD (*de novo*)	ID, Severe behavioral problems; knockout of *DEAF1* in the mice, memory deficits and increased anxiety-like behavior
KDM5C (MIM 314690)	A specific h3k4me3 and h3k4me2 demethylase, and acts as a transcriptional repressor through the RE-1-silencing transcription	AR	ID + Aggressive or violent behavior, Autism
UPF3 (MIM 300298)	A member of the nonsense-mediated mRNA decay complex	XL	ID, Autism, ADHD and childhood onset schizophrenia *UPF3B*-null mice: defect in sensorimotor gating

Table 7. Genes encoding proteins involved in metabolic processes

Gene	Function (www.omim.org)	Inheritance	Phenotype
HADH2 (MIM 300256)	17-beta-hydroxysteroid dehydrogenase X, a member of the short-chain dehydrogenase/ reductase superfamily	XL	ID, Abnormal behavior
NDST1 (MIM 600853)	Belongs to a family of bi-functional enzymes involved in heparan sulfate biosynthesis	AR	ID, Aggression, SIB

dividuals had moderate to severe ID, accompanied by behavioral disorders, mainly aggression and self-injurious behavior (SIB). A subsequent knockdown of NDST ortholog in Drosophila, sulfateless (SLF), resulted in a severely reduced learning index suggesting a possible role of SLF in fly long-term memory (Table 7).[159] Lenski, et al. reported a four-generation family with a unique clinical phenotype characterized by mild ID, choreoathetosis, and abnormal behavior apparently due to the reduced expression of the wild-type fragment resulting in decreased protein expression the gene *HADH2* encodingL-3-hydroxyacyl-CoA dehydrogenase II.[160]

Concluding remarks

An in-depth knowledge of a highly complex structure such as human brain calls for an ongoing pursuit of improved methods for identification of key role players in the maintenance and function of its intertwined networks. The advent of whole genome sequencing (WGS) as a primary tool for identification of causative genes in as massively heterogeneous phenomenon as ID, is paving the way to depict a bigger picture of the functional brain and possibly early pharmacological management.

Revelation of common circuitries based on observed similarities among neuropsychiatric diseases and animal models, as well as candidate gene identification and seeking their role in cognition and behavior would provide a useful tool, elucidating neurobiology of behavior impairments, including antisocial, neurodevelopment, and adaptive behavior disorders. With the synaptic plasticity as a major phenomenon in brain development, learning and behavior, it is not surprising to see functional deficits in many genes related to synaptic morphology, development and transmissions are accompanied by behavior impairments. Directing efforts to identify underlying causes of maladaptive behavior in individuals with cognitive impairment will be promoting measures to examine cases with ID and similar syndromes. In this review, we provide readers and researchers with the latest information and detailed analyses of reported behavior complaints observed in individual with cognitive problems. Functional analysis of potentially involved genes in cognition circuitries would be a starting point that will contribute further to our perception of complex neuropsychiatric networks, which might eventually result in the use of such genes to adapt molecular approaches to clinical diagnostics, family planning, risk prediction and prenatal diagnosis, treatment options, and setting therapeutic targets for high-risk groups of patients.

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