Regulatory Role of ADGRL3, PARK2, and CNTNAP2 in Neurodevelopmental Disorders

12

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Abstract

Adhesion G protein-coupled receptors (AGPCRs) are a 33-member subfamily of Class B GPCRs that control many physiological processes and are implicated in disease. AGPCRs play a role in cell-cell adhesion and neuron guidance via different proteins present in the surface of the cells and play a role in the development of glutamatergic synapses in the cortex. The most crucial function of Parkin RBR E3 ubiquitin protein ligase (PARK2) gene is unknown; moreover, the encoded protein is a component of a multiprotein E3 ubiquitin ligase complex that mediates the targeting of substrate proteins for proteasomal degradation. Mutations in the gene are known to cause Parkinson disease and autosomal recessive juvenile Parkinson disease. The researchers have shown that the Contactin-associated protein-like 2 (CNTNAP2) gene is associated with different symptoms of autism spectrum disorders (ASDs) and other neurodevelopmental disorders. The CNTNAP2 gene, coding for the cell adhesion glycoprotein Caspr2, is thought to be one of the major susceptibility genes for ASD. A large number of rare heterozygous missense CNTNAP2 variants have been identified in ASD patients. However, the intricate biochemical and molecular machinery contributing to the neurological disorders is still unknown. Here, we discuss the regulatory role of these proteins in neurodevelopmental disorders (NDDs).

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M. W. Qoronfleh et al. (eds.), *Proteins Associated with Neurodevelopmental Disorders*, Nutritional Neurosciences, https://doi.org/10.1007/978-981-15-9781-7_12

Keywords

Attention-deficit/hyperactivity disorder · ADHD · Orphan receptor · Unc-5 receptor · Netrin · ADGRL3 · PARK2 · CNTNAP2 and neurodevelopmental disorders

Abbreviations

ADGRL3	Adhesion G protein-coupled receptor L3
ADHD	Attention-deficit/hyperactivity disorder (ADHD)
aGPCRs	Adhesion G protein-coupled receptors
ARJP	Autosomal recessive juvenile parkinsonism
ASD	Autism spectrum disorder
CNTNAP2	Contactin-associated protein-like 2
DAT	Dopamine transporter
ECDs	Extracellular domains
ECR47	Evolutionarily conserved region 47
FLRT3	Fibronectin leucine-rich transmembrane protein 3
LPHN3	Latrophilin 3
PARK2	Parkin RBR E3 ubiquitin protein ligase
PD	Parkinson's disease
SNPs	Single-nucleotide polymorphisms
UNC5	Unc-5 netrin receptor
VGKC	Voltage-gated potassium channel complex

12.1 Latrophilin 3/Adhesion G Protein-Coupled Receptor L3 (LPHN3/ADGRL3)

The G protein-coupled receptor (GPCR) superfamily is the biggest group of cell membrane receptors. The seven transmembrane proteins transfer the external signals internally by connections between diverse stimuli like peptides, metabolites, light, hormones, ions, proteins, and N-terminal extracellular domains (ECDs). In humans, 33 members of the adhesion G protein-coupled receptor (aGPCR) family are present. Although the bulk of these is orphan receptors with unknown activities, many studies have shown that some members of this family play crucial roles in neurodevelopment, myelination, organogenesis, cancer progression, and angiogenesis. Significantly, human diseases have been related to mutations in various aGPCRs (Folts et al. 2019; Maraschi et al. 2014; Hu et al. 2016).

Attention-deficit/hyperactivity disorder (ADHD) disruptive behavior comorbidity, long-term prognosis, severity, and response to the treatment are predicted by variants in the ADGRL3 (LPHN3) gene (Acosta et al. 2016). The gene coding for latrophilin 3 (additionally known as adhesion G protein-coupled receptor L3 or

ADGRL3 or LPHN3) has been linked to ADHD vulnerability in independent ADHD samples (Bruxel et al. 2021) from human and animal studies. It was also demonstrated via fine mapping of a genetic linkage region for ADHD. ADGRL3 gene is expressed strongly in the caudate nucleus, amygdala, cerebral cortex, and cerebellum (Arcos-Burgos et al. 2010). During neurodevelopment, ADGRL3 and its ligands appear to play a crucial role in defining the connection rates between the primary neurons in the cortex (O'Sullivan et al. 2014) as well as neurotransmitter exocytosis and synaptic function. ADGRL3, also known as latrophilin 3 (LPHN3), is found in both the pre- and postsynaptic terminals of interneuron connections, suggesting that it might play a major role in the development and/or function of the synapse (Ribasés et al. 2011). As a result, changes in ADGRL3 expression might disrupt the proper establishment and maintenance of neural circuits, resulting in neurodevelopmental disorders (NDDs) like ADHD.

The creation of a trimeric complex with Unc-5 netrin receptor (UNC5) and fibronectin leucine-rich transmembrane protein 3 (FLRT3) by ADGRL3 mediates some of its actions at synaptic terminals. Both glutamatergic synapse formation and transcellular adhesion are aided by the above complex (Jackson et al. 2015). In mouse, zebrafish, and Drosophila, silencing or disruption of the ADGRL3 orthologue expression has consistently enhanced locomotor activity across species (Orsini et al. 2016; van der Voet et al. 2016), implying that this gene's function has been remarkably consistent throughout evolution. ADGRL3.1 and ADGRL3.2 are zebrafish paralogues of human ADGRL3, with ADGRL3.1 showing more particular expression patterns throughout embryonic development (Lange et al. 2012).

A prevalent ADGRL3 haplotype was connected to ADHD susceptibility in humans, a finding that was reproduced in both childhood and aged ADHD populations (Ribasés et al. 2011; Hwang et al. 2015; Kappel et al. 2017). An analysis of brain tissue transcriptomes in mice deficient in ADGRL3 reveals that gene expression for calcium signaling proteins and cell adhesion molecules is altered at distinct developmental time points, which in turn could influence neuronal function and structure (Martinez et al. 2016). ADGRL3 comprises an ultraconserved motif in the evolutionarily conserved region 47 (ECR47) that works as a transcriptional enhancer, according to an extensive investigation that included in silico, in vitro, and in vivo tests (Martinez et al. 2016). The authors also found that an ADHD risk haplotype (rs17226398, rs56038622, and rs2271338) lowered the enhancer activity in astrocytoma ad neuroblastoma cell lines by 40%. The rs2271338 risk allele interferes with the binding of the YY1 transcription factor to ECR47, which is critical for the function and development of the central nervous system. The haplotype causes the binding location of a crucial neurodevelopmental transcription factor to be disrupted.

Additionally, brain expression data indicate that ADGRL3 has maximum expression across infant and fetal stages and relatively high expression levels throughout life, suggesting that the gene is necessary for proper brain function (Martinez et al. 2016). YY1 knockdown, on the other hand, had no effect on ADGRL3 expression in differentiated cells, implying that ECR47 is only active during the developmental stages when the expression of ADGRL3 is higher (Martinez et al. 2016).

ADGRL3 interactions with other genes could also make an individual more prone to ADHD. ADGRL3 interacts with several genes that span a section on chromosome 11. Single-nucleotide polymorphisms (SNPs) in the 11q cluster interact with ADGRL3 SNPs to double the risk of ADHD and enhance the severity of the illness (Bruxel et al. 2015; Acosta et al. 2011; Puentes-Rozo et al. 2019). The genes present in the cascade play a vital role in brain development, confirming the neurological significance of ADHD.

12.2 Parkin RBR E3 Ubiquitin Protein Ligase (PARK2)

Parkin, a 465-amino acid protein, is a member of a multiprotein E3 ubiquitin ligase complex and targets the substrate proteins for degradation of proteasomes. It is essential for mitochondrial homeostasis and is encoded by the PARK2 gene. Mutations in PARK2 gene situated on 6q26 chromosome have been linked to Parkinson's disease, although structural changes have been reported in patients suffering from neurodevelopmental abnormalities, implying a widespread pathological effect in the brain's neurodegenerative and neurodevelopmental brain processes (Conceição et al. 2017). PARK2 gene is a neurodevelopmental gene that was first discovered as one of the reasons of early-onset Parkinson disease (Kitada et al. 1998) and has been linked to autism spectrum disorder (Glessner et al. 2009), schizophrenia (Xu et al. 2008), and attention-deficit/hyperactivity disorder (ADHD) (Jarick et al. 2014). According to Glessner et al., seven patients with ASD were shown to have a chromosome 6 copy number loss involving the PARK2 gene area (Glessner et al. 2009).

Parkin has a variety of substrates, demonstrating that it is a multifunctional protein engaged in various intracellular activities, including apoptosis regulation, management of mitochondrial integrity, and regulation of transcription (Charan and LaVoie 2015). Wild-type Parkin might affect cardiac health (Piquereau et al. 2013), Alzheimer's disease (Burns et al. 2009), cancer risk (Hu et al. 2016), multiple sclerosis (Witte et al. 2009), autism (Glessner et al. 2009), inclusion body myositis (Rosen et al. 2006), and leprosy (Mira et al. 2004). In addition, Parkin modulates a wide range of biological functions in both non-neuronal and neuronal cells (Charan and LaVoie 2015).

Parkinson's disease (PD) is a neurodegenerative movement illness due to the death of dopamine-producing neurons in the substantia nigra pars compacta. Damaged mitochondria may play a crucial role in PD pathophysiology, according to studies correlating PD to abnormalities in the electron transport chain (Venderova and Park 2012). PINK1 (PTEN-induced putative kinase protein 1 or PARK6) and Parkin (PARK2), two recessive PD genes, have provided solid insight into the role of damaged mitochondria in PD pathophysiology (Valente et al. 2004). PINK1 is the only protein kinase reported to have a mitochondrial targeting domain, while Parkin is a cytosolic E3 ubiquitin ligase. The two proteins are implicated in a similar pathway that promotes selective autophagy (mitophagy) of depolarized mitochondria and regulates mitochondrial quality control (Narendra et al. 2012).

Table 12.1 List of synaptic proteins which interact with Parkin

Binding member for Parkin	Impact on physiological processes	References
CDCrel-1/SEPT5_v1	Control of neurotransmitter release	Zhang et al. (2000)
Synphilin-1	Regulation of ubiquitination of α-synuclein	Chung et al. (2001)
Synaptotagmin XI	Docking and vesicle budding	Huynh et al. (2003)
GluK2	Regulation of kainate receptor currents	Maraschi et al. (2014)
DAT	Regulation of reuptake of dopamine	Jiang et al. (2004)

Parkin appears to play a role in cytoskeletal integrity, cell survival, and cell mitosis, among others (Moore 2006).

Patients suffering from NDDs like intellectual disability (ID), developmental delay (DD), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD) exhibit structural genetic changes in PARK2, known as copy number variants (CNVs) (Glessner et al. 2009; Jarick et al. 2014; Scheuerle and Wilson 2011; Mariani et al. 2013; Roberts et al. 2014). Mutations in the PARK2 gene reported in patients with autosomal recessive juvenile Parkinsonism (ARJP) might result in dysregulation of dopaminergic and glutamatergic synapses, leading to dopaminergic neuronal malfunction and death (Sassone et al. 2017).

The CDCrel-1 turnover, a protein that interacts with synaptic vesicles and governs their dynamics, is regulated by wild-type Parkin by interacting with ubiquitinate. Parkin mutations raise the amount of CDCrel-1, preventing neurotransmitter release (Zhang et al. 2000). Synphilin-1, a synaptic vesicle-binding protein whose physiological role is unknown, is likewise ubiquitinated by Parkin (Chung et al. 2001) and synaptotagmin XI, a presynaptic protein engaged in synaptic vesicle production and docking interactions to this protein (Huynh et al. 2003). Parkin has been shown to interact with proteins involved in synaptic vesicle release, implying that presynaptic Parkin might control dopamine release. Parkin associates to and ubiquitinates dopamine transporter (DAT), raising the DAT expression on the plasma membrane and promoting dopamine absorption (Jiang et al. 2004) (Table 12.1).

12.3 Contactin-Associated Protein-Like 2 (CNTNAP2)

The molecular pathways that govern central glutamatergic synapses are arising as common substrates in the etiology of mental diseases. In mice, Contactin-associated protein-like 2 (CNTNAP2), which is encoded by CNTNAP2, is critical for dendritic spine formation and produces disease-related abnormalities in its absence. Exon deletions, copy number variations, single-nucleotide variants, truncations, and polymorphisms in the CNTNAP2 gene have been linked to epilepsy, language difficulties, intellectual property, autism, and schizophrenia (Varea et al. 2015).

Table 12.2 Genes that have been associated with attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD)

Name of the genes	Associated disorder	Function of the gene	Phenotypical characteristics
CNTNAP2	ASD	Neuron-glia adhesion	Alteration of the dopaminergic system
ADGRL3	ADHD	Transcellular adhesion	Dysfunction of the dopaminergic system
PARK2	ASD ADHD	Mitochondrial quality control, E3 Ub protein ligase	Mitochondrial dysfunction

CNTNAP2 belongs to the neurexin family and is made of a 24-exon transcript that codes for the CASPR2 protein, which is involved in various neuronal activities such as dendritic arborization, neuronal migration, and synaptic transmission. Neurexins are cell adhesion proteins that play an essential role in synapse generation and synaptic property modulation. CASPR2 is responsible for the clustering of voltage-gated potassium channels and conduction of axon potentials at the juxtaparanodes in myelinated axons of both the spinal cord and the central nervous system (Varea et al. 2015; Flaherty et al. 2017). The strong expression of the protein in the Broca's area and other perisylvian regions is consistent with its novel role in social communication and normal language development (Bakkaloglu et al. 2008; Abrahams et al. 2007). In human neurodevelopmental impairments like autism, epilepsy, and intellectual disability, mutations in the CNTNAP2 gene coding CASPR2 have been reported. CASPR2, on the other hand, has been demonstrated to have a role in the localization of the voltage-gated potassium channel complex (VGKC), which comprises TAG-1, Kv1.1, and Kv1.2. This complex was identified in the node of Ranvier, the axon beginning segment, and the synapse, all of which are important for action potential propagation (Saint-Martin et al. 2018).

Axonal development was hindered, and synaptic abnormalities were identified in CNTNAP2 deletion neurons, suggesting that these factors may play a role in autism (Canali et al. 2018). Furthermore, mice with CNTNAP2 deletion exhibited stereotypic tendencies and communicative and social abnormalities, which are the main signs and symptoms of autism (Brumback et al. 2018; Scott et al. 2017). Thus, CNTNAP2 was deemed to be one of the most high-risk genes for ASD. The gene CNTNAP2 was one of the first to be linked to autism and epilepsy in Amish children (Strauss et al. 2006). Reduced presynaptic gamma-aminobutyric acid (GABA) and enhanced dopamine release in Cntnap4 knockout mice have been associated with severe, highly penetrant, recurring, and perseverative movements observed in human autism spectrum disorder patients (Li et al. 2018). Table 12.2 shows the overview of the genes that are associated strongly with ADHD and ASD.

12.4 Conclusions

ADGRL3 has putative roles in neuronal migration and synapse function. Various polymorphisms in ADGRL3 have been linked to an increased risk of attention-deficit/hyperactivity disorder (ADHD) in human studies. Impaired functioning of CNTNAP2 causes autism-related alterations in social interactions, stereotypic behavior, and sensory processing. Here, the authors have revealed present evidences for the contributions of ADGRL3, PARK2, and CNTNAP2 in NDDs such as ASD, Parkinson's diseases, and ADHA. PARK2 might be a pathological factor for NDDs. Essential functions of the above mentioned genes associated with NDDs might be important in the clinical disease presentation, and they act as suitable targets for therapeutic intervention.

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