

# Rho GTPase Regulators

Subjects: **Cell Biology**

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The Rho family GTPases are small G proteins that act as molecular switches shuttling between active and inactive forms. Rho GTPases are regulated by two classes of regulatory proteins, guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs). Rho GTPases transduce the upstream signals to downstream effectors, thus regulating diverse cellular processes, such as growth, migration, adhesion, and differentiation. In particular, Rho GTPases play essential roles in regulating neuronal morphology and function. Recent evidence suggests that dysfunction of Rho GTPase signaling contributes substantially to the pathogenesis of autism spectrum disorder (ASD). It has been found that 20 genes encoding Rho GTPase regulators and effectors are listed as ASD risk genes by Simons foundation autism research initiative (SFARI).

Rho GTPase

autism spectrum disorder

guanine nuclear exchange factor

GTPase-activating protein

animal model

behavior

## 1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by two core symptoms: (1) impaired social interaction and communication, and (2) repetitive or restricted interest and behaviors. The average global prevalence of ASD is ~0.62% [1], and studies in Europe and Asia have identified individuals with ASD with an average prevalence between 1% and 2% [2][3][4][5][6]. Statistics from CDC (Centers for Disease Control and Prevention)'s Autism and Developmental Disabilities Monitoring (ADDM) Network revealed that one in 59 children were diagnosed with ASD in United States in 2018 [7]. In addition, there is a high rate of co-occurring mental health disorders in ASD patients [8]. Meta-analysis of twin studies show that monozygotic twins have significantly higher concordance rate of ASD than dizygotic twins [9][10], thus the aetiology of ASD is closely related to genetic component. However, the genetic causes of ASD are very complex as a huge number of genes contribute to the pathogenesis of ASD. Therefore, databases of ASD-related genes, such as SFARI (Simons foundation autism research initiative) Gene [11][12] and AutDB (the autism gene database) [13], have been established. With the development of genome sequencing, increasing genes related to ASD have been identified. As of November 2019, more than 800 genes have been included in SFARI Gene [14] and more than 1000 genes have been listed in AutDB [15]. Among these ASD susceptibility genes, many converge on synapse regulation such as the regulation of development and maturation of synaptic contacts and synaptic transmission [16][17][18].

In the nervous system, precise neuronal connectivity depends on synapses. It is well known that dendritic spines, which are enriched with filamentous actin, are dynamic structures important for synapse formation, function and

plasticity [19]. Rho family GTPases are key regulators of the actin cytoskeleton that play critical roles in axonal outgrowth, dendritic spine morphogenesis, and synapse formation [20]. The Rho family GTPases, which belong to the Ras superfamily, are small G proteins sized ~20 KDa. Human Rho family GTPases include 20 members that can be classified into eight groups [21][22]. By cycling between GTP-bound active forms and GDP-bound inactive forms, Rho GTPases regulate a diverse array of cellular events, including the control of growth, migration, adhesion, and differentiation. Rho GTPase activity is regulated by two different kinds of regulatory protein: guanine nucleotide exchange factors (GEFs), which catalyze the replacement of GDP by GTP, enabling the GTPases to recognize downstream effectors, and GTP-activating proteins (GAPs), which negatively regulate GTPase activity by favoring the GDP-bound forms [19][23]. Rho GTPase activity regulation is a complex process as 82 GEFs [24][25] and 66 GAPs (of which 57 have a common GAP domain) [26] have been identified so far in humans. The complexity of Rho GTPase signaling is also contributed by their downstream effectors, as there are over 70 downstream effectors identified to be capable of transducing signals from Rho GTPases [27].

## 2. Rho Family GTPases and ASD

Rho GTPases themselves have been rarely reported as risk genes of ASD. The only evidence so far is the linkage of *RAC1* with ASD. Rac1 is an important Rho GTPase family member which regulates actin polymerization and spine remodeling through multiple signaling pathways, including PAKs (p21-activated kinases)-LIMK (LIM-domain-containing protein kinase)-cofilin [28], IRSp5 (insulin receptor substrate p53)-WAVE (Wiskott–Aldrich syndrome protein (WASP) family verprolin-homologous protein)-Arp2/3 [29][30], and PKA (protein kinase A) [31]. *RAC1*, encoding RAC1 and RAC1B, is a candidate gene for ASD listed in AutDB. Seven individuals with de novo mutations of *RAC1* were identified in patients of developmental disorders with divergent phenotypes [32]. One of these individuals displayed hyperactive behavior, two presented stereotypic movements, and one was diagnosed with autism [32]. Rac1 is highly expressed in embryonic cortex [33], and is ubiquitously expressed in the hippocampus, neocortex, thalamus, and cerebellum [34][35]. Rac1 is essential for the formation of three germ layers during gastrulation [36], and lack of which leads to embryonic lethality in *Rac1* knockout (KO) mice. To understand the brain function of Rac1, several *Rac1* conditional KO (cKO) mouse models have been constructed and studied. For instance, Foxg1-Cre mediated deletion of *Rac1* in the ventricular zone (VZ) of telencephalon [37][38][39], Nkx2.1-Cre-mediated deletion in medial ganglionic eminence (MGE) [40], and Nestin-Cre-mediated deletion in precursors of neurons and glia during early embryonic stage [29] were used to study the important roles of Rac1 for brain development. Moreover, three studies investigated the behavioral changes in *Rac1* cKO mouse models. Haditsch and colleagues generated a mouse model in which *Rac1* is deleted in pyramidal neurons by Cre under CamKIIa promoter to study the role of Rac1 in memory [41][42]. They demonstrated that loss of Rac1 in the hippocampus impairs long-term potentiation (LTP), and Rac1-deficient mice have impaired spatial memory and working or episodic-like memory [41]. They also found that the impaired working memory in these mice is due to prolonged memory retention or perseveration of the previously learned location [42]. Pennucci and colleagues generated a mouse model named Rac1N mice in which Rac1 is deleted in postmitotic neurons by Synapsin-I-Cre [43]. Rac1N mice show hyperactivity in several exploration tasks, impairment in spatial and working memory, and defects in retaining the context memory [43]. This study also reported failed synchronization of cortical networks in Rac1N

mice by quantitative electroencephalogram (EEG). Moreover, spontaneous inhibitory synaptic currents (sIPSCs) are decreased in CA1 glutamatergic pyramidal cells in these mice [43]. However, these findings only focus on memory-related behaviors, but not the typical ASD-related ones such as social behaviors.

### 3. Rho GTPase Effectors and ASD

It is well known that Rho GTPases act as molecular switches that transduce upstream signals to downstream effectors to engage specific signaling cascades. Once in the GTP-bound active forms, the conformations of effector-binding regions of Rho GTPases are changed to allow interaction with the effectors [44]. This interaction regulates the function of effectors, resulting in a series of cell responses to the initial stimuli. There are a large number of molecules involved in Rho GTPase signaling, and more than 70 proteins have been identified as potential effectors of RhoA, Rac1, and Cdc42 [27]. We examine the overlap between these effector genes and SFARI Gene and find the following six effectors as ASD-risk genes: *NCKAP1*, *CYFIP1*, *PAK2*, *ITPR1*, *PRKCA*, and *WASF1* (Table 1).

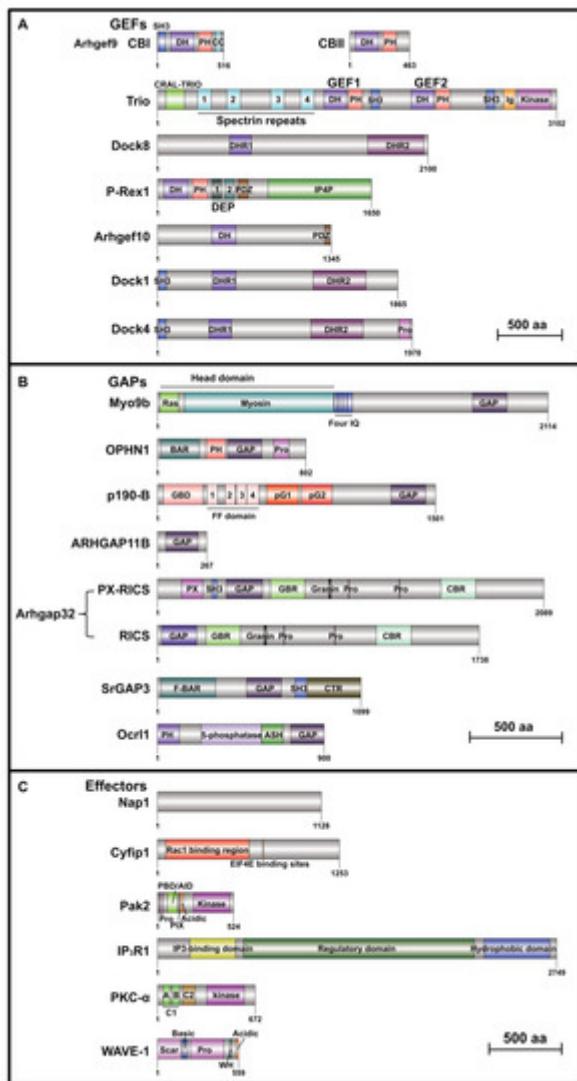
**Table 1.** Rho family GTPases involved in ASD.

ASD Candidate Gene	Gene Name	Chromosome Location	Genetic Category	SFARI Gene Score	Upstream/DOWNSTREAM Rho GTPase(s)
Rho GTPase GEF					
<i>ARHGEF9</i>	Cdc42 guanine nucleotide exchange factor (GEF) 9	Xq11.1-q11.2	Rare Single Gene Mutation, Syndromic	Category 1 (High Confidence)	CDC42
<i>TRIO</i>	Trio Rho guanine nucleotide exchange factor	5p15.2	Rare Single Gene Mutation, Syndromic	Category 1 (High Confidence)	RHOA, RAC1
<i>DOCK8</i>	Dedicator of cytokinesis 8	9p24.3	Rare Single Gene Mutation	Category 2 (Strong Candidate)	CDC42
<i>PREX1</i>	Phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 1	20q13.13	Genetic Association	Category 2 (Strong Candidate)	RAC1
<i>ARHGEF10</i>	Rho guanine nucleotide exchange factor 10	8p23.3	Rare Single Gene Mutation, Functional	Category 3 (Suggestive Evidence)	RHOA

ASD Candidate Gene	Gene Name	Chromosome Location	Genetic Category	SFARI Gene Score	Upstream/DOWNSTREAM Rho GTPase(s)
<i>DOCK1</i>	Dedicator of cytokinesis 1	10q26.2	Rare Single Gene Mutation	Category 3 (Suggestive Evidence)	RAC1
<i>DOCK4</i>	Dedicator of cytokinesis 4	7q31.1	Rare Single Gene Mutation, Genetic Association, functional	Category 3 (Suggestive Evidence)	RAC1
<b>Rho GTPase GAP</b>					
<i>MYO9B</i>	Myosin IXB	19p13.11	Rare Single Gene Mutation	Category 2 (Strong Candidate)	RHOA
<i>OPHN1</i>	Oligophrenin 1	Xq12	Rare Single Gene Mutation, Syndromic	Category 2 (Strong Candidate)	RHOA, RAC1, CDC42
<i>ARHGAP5</i>	Rho GTPase activating protein 5	14q12	Rare Single Gene Mutation	Category 3 (Suggestive Evidence)	RHOA, RAC1, CDC42
<i>ARHGAP11B</i>	Rho GTPase activating protein 11B	15q13.2	Rare Single Gene Mutation	Category 3 (Suggestive Evidence)	Unknown
<i>ARHGAP32</i>	Rho GTPase activating protein 32	11q24.3	Rare Single Gene Mutation, Functional	Category 3 (Suggestive Evidence)	RHOA, RAC1, CDC42
<i>SRGAP3</i>	SLIT-ROBO Rho GTPase activating protein 3	3p25.3	Rare Single Gene Mutation	Category 3 (Suggestive Evidence)	CDC42, RAC1
<i>OCRL</i>	Oculocerebrorenal syndrome of Lowe	Xq26.1	Rare Single Gene Mutation, Syndromic	Syndromic	CDC42, RAC1
<b>Rho GTPase Effector</b>					
<i>NCKAP1</i>	NCK-associated protein 1	2q32.1	Rare Single Gene	Category 1 (High)	RAC1

ASD Candidate Gene	Gene Name	Chromosome Location	Genetic Category	SFARI Gene Score	Upstream/DOWNSTREAM Rho GTPase(s)
			Mutation	Confidence)	
<i>CYFIP1</i>	Cytoplasmic FMR1 interacting protein 1	15q11.2	Rare Single Gene Mutation, Genetic Association, Functional	Category 2 (Strong Candidate)	RAC1
<i>PAK2</i>	p21 (RAC <sup>[46]</sup> activated kinase 2	3q29	Rare Single Gene Mutation <sup>[47][48][49]</sup>	Category 2 (Strong Candidate)	CDC42, RAC1
<i>ITPR</i> <sup>[50][51]</sup>	Inositol 1,4,5-trisphosphate receptor type 1	3p26.1	Rare Single Gene Mutation	Category 3 (Suggestive Evidence)	RHOA
<i>PRKCA</i>	Protein kinase C alpha <sup>[53]</sup>	17q24.2	Rare Single Gene Mutation	Category 3 (Suggestive Evidence)	RHOA, RAC1, CDC42 <sup>[53]</sup>
<i>WASF1</i>	WAS protein family member 1	6q21	Syndromic	Syndromic	RAC1

cortex <sup>[54]</sup>. YOKOYA and colleagues found that knockdown of endogenous Nap1 leads to defective neuronal differentiation in mouse cortical neurons <sup>[54]</sup>. They then generated a Nap1 mutant mouse line in which the N-terminal 898 aa of Nap1 fused with a 1291 aa β-geo reporter is expressed instead of the full-length protein <sup>[54]</sup>. However, these Nap1 mutant mice are embryonic lethal from E8.5–E10.5 due to neural tube and neuronal differentiation defects <sup>[54]</sup>. Therefore, mouse models of Nap1 deficiency are still absent for the investigation of Nap1 on regulating neural behaviors.



**Figure 1.** Schematics of protein domain structures of 20 ASD-related RhoGEFs, RhoGAPs, and Rho effectors. **(A)** Seven ASD-related RhoGEF protein domain architectures. Arhgef9 (which has two variants, CB I and CB II), Trio, P-Rex1, and Arhgef10 belong to Dbl family, which is characterized by a DH domain (dark violet) and a PH domain (light pink). Dock8, Dock1, and Dock4 belong to Dock family, which contains two main domains, DHR1 domain (dark orchid) and DHR2 domain (dark magenta). **(B)** Seven ASD-related RhoGAP protein domain architectures. In addition to a common catalytic GAP domain (purple), most RhoGAPs have multiple other functional domains. **(C)** Six ASD-related Rho effector protein domain architectures. All protein structures are generated using DOG 2.0 (Domain Graph, version 2.0) [55] based on corresponding mouse protein sequences except ARHGAP11B, for which human protein structure is shown as no homologs exist in rodents. Scales represent amino acid numbers of 500. AID, Autoinhibitory Domain; ASH, ASPM/SPD2/Hydin; BAR, Bin/Amphiphysin/Rvs; C1, binding site of diacylglycerol (DAG); C2, binding site of  $\text{Ca}^{2+}$ ; CBR,  $\beta$ -catenin-binding region; CC, coiled-coil; CRAL-TRIO, cellular retinaldehyde-binding protein and TRIO guanine exchange factor; CTR, C-terminal region with proline-rich; DEP, Disheveled, EGL-10, Pleckstrin; DH, Dbl Homology; DHR1, Dock homology region 1; DHR2, Dock homology region 2; F-BAR, Fes-Cip4 homology Bin/Amphiphysin/Rvs; FF, domain with two conserved phenylalanine residues; GAP, GTPase-activating proteins; GBD, guanosine triphosphate (GTP)-binding; GBR, GABARAP-binding region; Ig, immunoglobulin; IP4P, inositol polyphosphate 4-phosphatase; IQ, short calmodulin-binding motif

containing conserved isoleucine and glutamine residues; PBD, p21-binding domain; PDZ, PSD95/SAP90, DlgA, ZO-1; pG1, pseudoGTPase domain 1; pG2, pseudoGTPase domain 2; PH, Pleckstrin-Homology; PIX, Pak-interacting exchange factor; Pro, proline-rich; PX, phox homology; Scar, Scar homology; SH3, Src homology 3; WH, WASF homology.

### 3.2. CYFIP1 (SFARI Gene Score: 2, Strong Candidate)

Cytoplasmic FMR1 interacting protein 1 (Cyfip1), also named Shyc and Sra1, is a Rac1-interacting protein and a partner of the WAVE complex that regulates actin filament. *CYFIP1* is located on chromosome 15q11.2. Several studies have reported that patients with 15q11.2 microdeletions and microduplications between breakpoints 1 and 2, which encompass several genes including *CYFIP1*, are diagnosed with neurodevelopmental disorders including ASD, ID, SCZ, attention-deficit/hyperactivity disorder (ADHD), and obsessive-compulsive disorder (OCD) [56][57][58][59]. A paternally inherited rare variant of *CYFIP1* is found in an autistic patient with a de novo *SHANK2* deletion [60]. Another paternally inherited rare variant of *CYFIP1* is found in a study on high functioning ASD patients [61]. Additionally, SNPs in *CYFIP1* were reported to correlate with ASD in two studies [62][63]. A study on *CYFIP1* mRNA expression in human dorsolateral prefrontal cortex revealed higher expression of *CYFIP1* mRNA in ASD and classical autism patients, and identified several common variants of *CYFIP1* in these patients [64]. A recent study also demonstrated significant increase in *CYFIP1* transcripts in the peripheral blood of ASD patients [65]. All these clinical findings reveal that altered *CYFIP1* dosage may contribute to the pathology of ASD. Cyfip1 has been shown to interact with Rac1, Fragile X mental retardation 1 (FMRP), and eukaryotic translation initiation factor 4E (EIF4E) [66][67] (Figure 1C). Cyfip1 is widely expressed in multiple tissues but not liver during development and is highly enriched in the hippocampus, cerebral cortex, cerebellum, olfactory bulb, and lateral septum in the adult brain [68]. Levels of Cyfip1 are high in the cortex and cerebellum at the stages of postnatal development, peaked at P23 and slightly decreased afterwards [69].

Four different strategies have been used for generation of *Cyfip1* KO mice. However, because *Cyfip1* is very important for early embryonic development, none produce homozygous *Cyfip1* KO mice. Therefore, *Cyfip1* HET mice are used for studying behavioral and neural phenotypes in these studies. The first mouse model was generated by mutagenesis with a gene trap vector inserted into intron 1 of *Cyfip1*. There are no *Cyfip1* KO embryos in breeding [70]. *Cyfip1* HET mice display normal learning and memory abilities in several memory tests, but show more rapid extinction in inhibitory avoidance test, a test for hippocampus-dependent memory [70] (Table 2; Supplementary Table S1, supplementary could be found in <https://www.mdpi.com/2073-4409/9/4/835#supplementary>). These results indicate that the accuracy of memory processing in HET mice is much poorer. *Cyfip1* HET mice show increased mGluR-dependent LTD and abnormal presynaptic function in hippocampal slices [70][71]. The second one is generated by deleting exons 4–6 of *Cyfip1*. Inbred from *Cyfip1*<sup>HET</sup> mice, fertilized *Cyfip1* KO oocytes are detectable in blastocyst stage [72]. The KO embryos can survive until E8.5, but become lethal due to complete developmental failure [72]. The *Cyfip1*<sup>HET</sup> mice show absence of interest for social cues and deficits in motor learning [73] (Table 2; Supplementary Table S1). The third one is generated by deleting exon 5 of *Cyfip1*, and the *Cyfip1* homozygous KO embryos die before E9.5 [74]. Moreover, the difference between the maternal (m-/p+) and paternal (m+/p-) deficiency of *Cyfip1* was investigated.

Interestingly, *Cyfip1* m-/p+ mice only display hypoactivity, whereas *Cyfip1* m+/p- mice display increased freezing in cued fear conditioning and abnormal transitions in zero-maze test [74] (Table 2; Supplementary Table S1). Both *Cyfip1* m-/p+ mice and *Cyfip1* m+/p- mice show reduced field EPSC and increased PPF in hippocampal CA1 region, and enhanced mGluR-dependent LTD is observed in *Cyfip1* m+/p- mice hippocampal CA1 neurons [74]. The fourth one is generated by inserting a gene trap cassette between exon 12 and 13 of *Cyfip1*. *Cyfip1*<sup>+/−</sup> mice display impaired motor coordination, deficient sensory processing/novelty seeking behavior, reduced PPI, and decreased sensory motor gating [75] (Table 2; Supplementary Table S1), recapitulating some ASD and SCZ-like behavioral phenotypes. *Cyfip1*<sup>+/−</sup> mice show reduced spontaneous neuronal activity and presynaptic function in cortical slices [75]. Besides the whole-body mutant mice, one *Cyfip1* cKO mouse model (*Cyfip1*<sup>NEX</sup> cKO mice) has been generated, in which exon 4–6 of *Cyfip1* was deleted in forebrain excitatory neurons by NEX-Cre. These mice are viable until adulthood with no obvious abnormalities [76]. *Cyfip1*<sup>NEX</sup> cKO mice show increased mIPSC amplitude in hippocampal CA1 neurons and display similar deficits in dendrite morphology and spine maturation to those described in *Cyfip1* haploinsufficient models [76]. There is also a *Cyfip1* mutant rat model generated by CRISPR/Cas9 technology, in which a 4 bp heterozygous deletion is introduced in exon 7 of *Cyfip1*, causing premature stop of the protein [77]. These *Cyfip1* haploinsufficient rats exhibit normal learning ability during all behavioral tests, but show deficits in behavioral flexibility [77] (Table 2; Supplementary Table S1). As increased transcript levels of *CYFIP1* is found in some ASD patients, two transgenic (Tg) *Cyfip1* mouse lines (Tg line 1 and Tg line 2) were generated by overexpressing human *CYFIP1*. mRNA of human *CYFIP1* was increased in the cortex and hippocampus of both Tg lines; *Cyfip1* protein is also increased in the two brain regions of Tg line 1 and the hippocampus of Tg line 2, but not in the cortex of Tg line 2 [78]. Behaviorally, Tg line 2 mice display subtle defects of spatial learning memory and obvious increased fear response in contextual and cued fear conditioning test, whereas Tg line 1 mice show normal spatial learning memory and increased freezing only to the tone in the novel context during fear conditioning test [78] (Table 2; Supplementary Table S1). However, both Tg lines show no deficits in core ASD-related behaviors such as social and repetitive behaviors [78] (Table 2; Supplementary Table S1). Together, *Cyfip1* deficient mice or rats recapitulate core features of ASD, whereas *Cyfip1* Tg mice may not be appropriate ASD models.

**Table 2.** Summary of ASD-related behavior tests in Rho guanine nucleotide exchange factor (GEF), GTPase-activating protein (GAP), and effector mouse models.

Gene	Mouse Model	Core Symptoms				Comorbidities			
		Social Related Behavior	Language Communication	Repetitive Behavior	Anxiety and Depression	Learning and Memory	Locomotion and Motor Coordination	Schizophrenia and Reference Coordination	Reference and Epilepsy
Summary of ASD-related behavior tests in Rho GEF mouse models									
ARHGEF9	Arhgef9 KO mice *	NT <sup>1</sup>	NT	NT	Anxiety ↑	Spatial learning and memory ↓	Activity −	NT	[79]

Gene	Mouse Model	Core Symptoms				Comorbidities			
		Social Related Behavior	Language Communication	Repetitive Behavior	Anxiety and Depression	Learning and Memory	Basic locomotion	Schizophrenia and Motor Coordination	Reference and Epilepsy
	<i>Emx1-Trio<sup>-/-</sup></i> mice #	NT	NT	NT	NT	Spatial learning and memory ↓ Fear memory ↓	NT	NT	[80]
TRIO	<i>NEX-Trio<sup>+/-</sup></i> mice &	Social preference ↓	NT	Nestlet shredding (M <sup>2</sup> , ↑; F <sup>3</sup> , -)	Anxiety ↑ Depression -	Object recognition memory -	Activity ↓ Motor coordination ↓	Prepulse inhibition -	[81]
	<i>NEX-Trio<sup>-/-</sup></i> mice &	Social preference ↓	NT	Nestlet shredding (M, ↑; F, -)	Anxiety (M, ↑; F, -) Depression ↑	Object recognition memory -	Activity ↑ Motor coordination ↓	Prepulse inhibition (M, ↓; F, -)	[81]
PREX1	<i>Prex1<sup>-/-</sup></i> mice *	Social preference ↓ Social learning and memory ↓ Olfactory function -	Ultrasonic vocalizations (pup) ↓	Grooming ↑	Anxiety -	Reversal learning ↓ Fear memory ↓ Object recognition memory -	Activity - Motor coordination -	Prepulse inhibition -	[82]
	<i>Arhgef10</i> KO mice *	Sociability and social novelty preference ↓	NT	NT	Anxiety ↓ Depression ↓	Spatial learning and memory -	Activity ↑	Prepulse inhibition -	[83]
DOCK4	<i>Dock4</i> KO mice &	Social novelty preference ↓	Ultrasonic vocalizations (pup) ↓	Stereotyped circling (~9% F; M, -) Marble burying (M, -, F, NT) Grooming (M, -, F, NT)	Anxiety ↑	Object recognition memory (F, ↑; M, -) Spatial memory (M, ↓; F, -) Working memory (M, ↓; F, -)	Activity (~9% F, ↑; M, -)	NT	[84]
	<i>Dock4</i> HET mice &	Social novelty preference (F, ↑; M, -)	Ultrasonic vocalizations (pup) -	Stereotyped circling (~1.7% F; M, -)	Anxiety -	Object recognition memory - Spatial	Activity (~1.7% F, ↑; M, -)	NT	[84]

Gene	Mouse Model	Core Symptoms				Comorbidities					
		Social Related Behavior	Language Communication	Repetitive Behavior	Anxiety and Depression	Learning and Memory	Basic locomotion	Schizophrenia and Motor Coordination	Reference and Epilepsy		
				Marble burying (M, $\neg$ ; F, NT) Grooming (M, $\neg$ ; F, NT)		memory (F, $\downarrow$ ; M, $\neg$ ) Working memory $\neg$					
		Summary of ASD-related behavior tests in Rho GAP mouse models									
OPHN1	<i>Ophn1</i> <sup>-/-</sup> mice *	Aggressivity $\downarrow$ Social memory $\neg$ Olfactory function $\downarrow$	NT	NT	Anxiety $\neg$	Working, object recognition, and spatial learning and memory $\downarrow$ Fear memory extinction $\downarrow$ Vicarious trial and error (VTE) behavior $\downarrow$	Activity $\uparrow$ Motor coordination $\neg$ Behavioral lateralization $\downarrow$	NT	[85][86][87] [88][89]		
ARHGAP32	<i>PX-RICS</i> <sup>-/-</sup> mice (M were used in most behavior tests unless otherwise stated)	Social novelty preference $\downarrow$ social interaction $\downarrow$	Ultrasonic vocalizations (M and F, $\downarrow$ )	Grooming $\uparrow$ Marble burying $\uparrow$	NT	Reversal learning $\downarrow$ Fear memory $\downarrow$	Motor coordination $\downarrow$	Epilepsy (Severe progressive seizures)	[90][91]		
	<i>PX-RICS</i> <sup>+/-</sup> mice (M were used in most behavior tests unless otherwise stated)	Social novelty preference $\downarrow$ social interaction $\downarrow$	Ultrasonic vocalizations (M and F, $\neg$ )	Grooming $\neg$ Marble burying $\uparrow$	NT	Reversal learning $\neg$	Motor coordination $\neg$	NT	[90]		
SRGAP3	<i>WRP</i> <sup>-/-</sup> mice &	NT	NT	NT	Anxiety $\neg$	Object recognition and long-term memory $\downarrow$ Spatial and reversal learning $\downarrow$ Working memory $\neg$	Activity $\neg$ Motor coordination $\neg$	NT	[92]		

Gene	Mouse Model	Core Symptoms					Comorbidities			Reference
		Social Related Behavior	Language Communication	Repetitive Behavior	Anxiety and Depression	Learning and Memory	Basic locomotion and Motor coordination	Schizophrenia and Epilepsy		
DUBLIN 111	<i>WRP</i> <sup>+/-</sup> mice & [73]	NT	NT	NT	Anxiety -	Object recognition and long-term memory ↓ Spatial and reversal learning ↓ Working memory -	Activity - Motor coordination -	NT	[70]	mGluR5 blockers
	<i>SrGAP3</i> <sup>-/-</sup> mice & [73]	Social interaction ↓	HET	NT	Marble burying (M, -; F, NT)	Anxiety - Working memory ↓ Spatial and object recognition memory - Fear memory ↑	Activity (M, ↓; F, -)	Prepulse inhibition (F, ↓; M, -)	[93][94]	HET mice, development
	<i>Ocr1</i> <sup>-/-</sup> mice *	NT	NT	NT	NT	Passive avoidance preference -	Activity - Motor coordination ↓	NT	[95]	
Gene	Mouse/Cellular Model	Therapeutic Type		Therapeutic Strategy			Result		Reference	
TRIO	<i>Trio</i> deficient neurons	Pharmacological		Rp-cAMPS treatment (100 μM)			Increased dendritic spine density reversed		[81]	
		Non-pharmacological		PDE4A5 overexpression			D-serine (for electrophysiology: 20 μM; for mouse: 0.8 g/kg i.p. (intraperitoneal))		NMDAR-LTD restored; disruptive social novelty corrected	
P-REX1	<i>Prex1</i> <sup>-/-</sup> mice	Non-pharmacological		WT P-Rex1 or WT Rac1 overexpression (in CA1 pyramidal neurons)			NMDAR-LTD restored; disruptive social novelty and reversal learning corrected		[82]	
DOCK4	<i>Dock4</i> KO mice	Pharmacological		D-cycloserine (DCS, 20 mg/kg i.p.)			Social novelty restored		[84]	
		Non-pharmacological		WT Rac1 overexpression (in CA1 region)			Social novelty and synaptic transmission (mEPSC and LTP) restored		[102]	
	<i>Dock4</i> knockdown neurons	Non-pharmacological		WT Rac1 overexpression			Decreased dendritic spine		[102]	

Gene	Mouse/Cellular Model	Therapeutic Type	Therapeutic Strategy	Result	Reference
<i>OPHN1</i>	<i>Ophn1</i> <sup>-ly</sup> mice	Pharmacological	Rp-cAMPS (bilaterally infused into PFC; 10 µg/µL; 300–400 nl)	density reversed	
			Fasudil (dissolved in daily drinking water at 0.65 mg/mL for 3 weeks)	Cognitive dysfunction in Y-maze ameliorated	[89]
				Spine morphology in olfactory bulbs, frequency and amplitude of mIPSC in olfactory neurons, and olfactory behaviors rescued	[87]
				Fear memory extinction restored	[88]
<i>ARHGAP32</i>	<i>PX-RICS</i> <sup>-/-</sup> mice	Pharmacological	Fasudil (orally a daily dose of 3 mg for 3 months)	Locomotor activity and object recognition memory restored; abnormal brain morphology ameliorated	[86]
			Clonazepam (CZP, 0.03 mg/kg i.p.)	Deficits of social preference, reversal learning, and cued fear learning memory reversed	[90][91]
<i>CYFIP1</i>	<i>Cyfip1</i> HET mice hippocampal slices	Pharmacological	LY367385 (100 µM) and MPEP (2-Methyl-6-phenylethynyl pyridine), (10 µM) (Incubated in slices)	mGluR-LTD normalized to control levels	[70]

Gene	Mouse/Cellular Model	Therapeutic Type	Therapeutic Strategy	Result	Reference
	<i>Cyfip1</i> <sup>HET</sup> mice	Non-pharmacological	Motor training (at postnatal days 40, 50, and 51)	Motor deficits alleviated	[73]
PAK2	<sup>[103]</sup> <i>Pak2</i> <sup>+/−</sup> mice	Non-pharmacological	p-cofilin peptide (15 pmol/g i.v. (intravenous))	Social behaviors moderately improved	[104] [97]
<i>ITPR1</i>	<sup>[105]</sup> <i>Wnt1-Cre;Itpr1</i> <sup>fl/fl</sup> mice <sup>[97]</sup>	Pharmacological Non-pharmacological	CNQX (5 mM; infused into the cerebellum; 0.5 µL/min for 20 min) Mating with <i>Lurcher</i> mice ( <i>GluD2</i> <sup>LC/+</sup> )	Dyskinesia ameliorated Dystonic movements eliminated	[106] [100]

PBD (p21-binding domain) in the N-terminal region, a kinase domain at the C-terminus, an acidic region, and a PIX gender was not mentioned; <sup>1</sup> NT: not tested; <sup>2</sup> M: male mice; <sup>3</sup> F: female mice; <sup>↑</sup> is increased and <sup>↓</sup> is decreased; <sup>−</sup> (Pak-interacting exchange factor) binding site <sup>[107][108][109]</sup> (Figure 1C). Pak2 is ubiquitously expressed in multiple tissues <sup>[110]</sup>. More detailed information is shown in [Supplementary Table S1](#).

Human PAK2 shows high expression levels in the brain during the fetal period and low levels after birth. Mouse Pak2 is also down-regulated at the postnatal development in the cortex <sup>[97]</sup>. Loss of *Pak2* leads to embryonic lethality at ~E8 <sup>[110][111][112]</sup>. Therefore, a recent study used *Pak2*<sup>+/−</sup> mice to investigate the behavioral and neural functional changes caused by *Pak2* haploinsufficiency. This study revealed that *Pak2*<sup>+/−</sup> mice display repetitive and stereotyped behaviors, impaired social interaction, social avoidance, reduced social preference index, and disruptive social memory <sup>[97]</sup> ([Table 2](#); [Supplementary Table S1](#)). *Pak2*<sup>+/−</sup> mice also exhibit decreased LTP in hippocampal CA1 region neurons <sup>[97]</sup>. Mechanistically, phosphorylation of both LIMK1, a major downstream target of group I PAKs, and its substrate cofilin were markedly decreased, suggesting abnormal LIMK1/cofilin-mediated actin polymerization in adult *Pak2*<sup>+/−</sup> mice cortex <sup>[97]</sup>. To normalize endogenous p-cofilin levels in the cortex and hippocampus, a p-cofilin peptide was intravenously injected into adult *Pak2*<sup>+/−</sup> mice as a substrate to compete with endogenous p-cofilin for phosphatases. As a result, this peptide moderately improved social behaviors but not repetitive behaviors in adult *Pak2*<sup>+/−</sup> mice <sup>[97]</sup> ([Table 3](#)).

### 3.4. ITPR1 (SFARI Gene Score: 3, Suggestive Evidence)

Inositol 1,4,5-trisphosphate receptor type 1, also known as IP<sub>3</sub>R1, is a RhoA effector. IP<sub>3</sub>R1 is a member of IP<sub>3</sub>Rs, which are Ca<sup>2+</sup> release channels on the endoplasmic reticulum. *ITPR1* is located on chromosome 3p26.1. Three de novo missense variants in *ITPR1* are found in ASD probands from WES studies <sup>[47][50][48]</sup>. In addition, a study on autism risk genes in probands from the Autism Clinical and Genetic Resources in China (ACGC) identified one maternally and one paternally inherited missense variant of *ITPR1* <sup>[113]</sup>, and another variant is found in patients with NDDs <sup>[114]</sup>. IP<sub>3</sub>R1 has three main domains including a large N-terminal IP<sub>3</sub>-binding domain, a short C-terminal hydrophobic domain, and an intervening regulatory domain <sup>[115]</sup> (Figure 2C). The expression of IP<sub>3</sub>R1 is increased during embryogenesis <sup>[116]</sup>. Moreover, IP<sub>3</sub>R1 is predominately expressed in the nervous system <sup>[117][118]</sup> and is expressed in a wide range of brain regions including the cerebellum, cerebral cortex, hippocampus, olfactory bulb,

globus pallidus, and striatum [117]. It was reported that homozygous *IP<sub>3</sub>R1*-deficient mice mostly die during the embryonic stage, and the born mice have severe ataxia and seizures and die at around P21 [119]. *IP<sub>3</sub>R1*<sup>+/−</sup> mice also show deficits in motor coordination [98] (Table 2; Supplementary Table S1). To study the neural function of *IP<sub>3</sub>R1*, several *IP<sub>3</sub>R1* brain cKO mouse lines have been generated. A study reported that *L7-Cre;Itpr1*<sup>flox/flox</sup> mice, in which *Itpr1* is deleted in Purkinje cells, exhibit cerebellar ataxia at around 6 weeks and severe ataxia at 8 weeks after birth [99] (Table 2; Supplementary Table S1). *L7-Cre;Itpr1*<sup>flox/flox</sup> mice could survive to adulthood, but display abnormal motor learning ability [99] (Table 2; Supplementary Table S1). In another study, three cKO lines were used, in which *Itpr1* deletion was restricted to the cerebral cortex and hippocampus (*Emx1-Cre;Itpr1*<sup>flox/flox</sup> mice), the cerebellum and brainstem (*Wnt1-Cre;Itpr1*<sup>flox/flox</sup> mice), and the caudate putamen and globus pallidus (*Gpr88-Cre;Itpr1*<sup>flox/flox</sup> mice) [100]. The *Emx1-Cre;Itpr1*<sup>flox/flox</sup> mice and *Gpr88-Cre;Itpr1*<sup>flox/flox</sup> mice were born normally and showed normal growth patterns until adulthood, without apparent dyskinesia like total *Itpr1*<sup>−/−</sup> mice. However, *Wnt1-Cre;Itpr1*<sup>flox/flox</sup> mice began to show ataxia at around P9, and exhibited dyskinesia from 2 weeks after birth [100] (Table 2; Supplementary Table S1). *Wnt1-Cre;Itpr1*<sup>flox/flox</sup> mice show abnormal cerebellar Purkinje cell (PC) firing patterns, due to altered PC activity [100]. *Itpr1* deficiency induces a series of abnormal electrophysiological features, including failed LTD in the PCs [120], and excessive LTP induction, attenuated depotentiation and LTP suppression, and altered presynaptic activity in hippocampal CA1 neurons [121][122]. However, typical ASD-related behaviors such as social and repetitive behaviors have not been investigated using these mice.

As enhanced PC activity and dystonia were observed in *Wnt1-Cre;Itpr1*<sup>flox/flox</sup> mice, pharmacological inactivation of cerebellar activity by AMPA receptor antagonist (CNQX) infusion was examined for therapeutic effects. Indeed, CNQX ameliorates the dyskinesia in these mice [100] (Table 3). Furthermore, dystonic movements were completely absent in *Wnt1-Cre;Itpr1*<sup>flox/flox</sup> mice with genetic deletion of cerebellar PCs, achieved by mating *Wnt1-Cre;Itpr1*<sup>flox/flox</sup> mice with *Lurcher* mice (*GluD2*<sup>LC/+</sup>) to kill most of PCs by a mutation of the delta 2 glutamate receptor (*GluD2*) [100] (Table 3).

### 3.5. PRKCA (SFARI Gene Score: 3, Suggestive Evidence)

Protein kinase C alpha (PKC-α) is a member of lipid-sensitive serine/threonine protein kinases that regulate various cellular functions including proliferation, migration, adhesion, differentiation, and apoptosis. PKC-α appears to be a common downstream effector of RhoA, Cdc42, Rac1. *PRKCA* is located on chromosome 17q24.2. In two WES studies, three de novo missense variants in *PRKCA* were reported in ASD probands [47][48]. PKC-α has a variable regulatory domain at the N-terminus consisting of a C1 domain and a C2 domain, which function as the binding sites of diacylglycerol (DAG) and  $\text{Ca}^{2+}$ , respectively. PKC-α also has a highly conserved kinase domain at the C-terminus comprised by a smaller ATP-binding loop and a substrate-binding site [123][124] (Figure 1C). PKC-α is ubiquitously expressed in all tissues, including the heart, adrenal gland, testis, lung, kidney, spleen, and liver, and is also widespread in various regions of the brain [125]. PKC-α is enriched in both neuronal and glial cultured cells [125]. A *PKC-α* KO mouse line has been generated, which appears to be normal with regard to external characteristics, viability, and fertility [126]. However, ASD-related behavioral analysis of these mice has not been reported.

### 3.6. WASF1 (SFARI Gene Score: S, Syndromic)

The Rac1 effector WAS protein family member 1 (WASF1), also known as WAVE-1/Scar1, is a member of the WASP-family. *WASF1* is located on chromosome 6q21. Using exome sequencing and whole-genome sequencing, three de novo truncated mutations of *WASF1* were reported in five unrelated individuals, all of whom presented ID with autistic features and seizures [127]. This is the only study so far that has reported the relationship between *WASF1* and ASD. WAVE-1 is composed by a Scar homology domain, a basic domain, a proline-rich region, a WASF homology (WH) domain, and an acidic domain [128] (Figure 1C). In human tissues, the expression of WAVE-1 is restricted to the brain [129]. Mouse study reveals that WAVE-1 shows high expression in the hippocampus, cortex, hypothalamus, amygdala, and cerebellum [101][130][131]. Two mouse lines of homozygous *Wave1* deletion are reported to be either postnatal lethal [130] or reduced in body size of offspring [101]. Behavioral analysis using *Wave1* KO mice (WAVE-1 null mice) generated by the second strategy showed hypoactivity, impaired motor coordination and balance, reduced anxiety levels, and defected spatial, nonspatial, and emotional learning and memory in the mice [101] (Table 2; Supplementary Table S1).

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