The Ras Superfamily of Small GTPases in Non-neoplastic Cerebral Diseases

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The small GTPases from the Ras superfamily play crucial roles in basic cellular processes during practically the entire process of neurodevelopment, including neurogenesis, differentiation, gene expression, membrane and protein traffic, vesicular trafficking, and synaptic plasticity. Small GTPases are key signal transducing enzymes that link extracellular cues to the neuronal responses required for the construction of neuronal networks, as well as for synaptic function and plasticity. Different subfamilies of small GTPases have been linked to a number of non-neoplastic cerebral diseases such as Alzheimer’s disease (AD), Parkinson’s disease (PD), intellectual disability, epilepsy, drug addiction, Huntington’s disease (HD), amyotrophic lateral sclerosis (ALS) and a large number of idiopathic cerebral diseases. Here, we attempted to make a clearer illustration of the relationship between Ras superfamily GTPases and non-neoplastic cerebral diseases, as well as their roles in the neural system. In future studies, potential treatments for non-neoplastic cerebral diseases which are based on small GTPase related signaling pathways should be explored further. In this paper, we review all the available literature in support of this possibility.

Keywords: small GTPases, Ras superfamily, Rho subfamily, Rab subfamily, Arf subfamily, Ran subfamily, non-neoplastic cerebral diseases

INTRODUCTION

Small GTPases are defined by their basic biochemical activity of binding GTP and hydrolyzing it to GDP, which is called the guanosine triphosphate (GTP)/guanosine diphosphate (GDP) cycle (Bourne et al., 1991). Although similar to the heterotrimeric G protein α subunits in biochemistry and function, small GTPases function as monomeric G proteins (Claing, 2013). In addition to their high affinity and hydrolysis activity for GTP, small GTPases have two states, a GTP-bound state and a GDP-bound state. The activated small G-proteins are mainly regulated by three crucial factors: Guanosine nucleotide dissociation inhibitors (GDIIs), guanine nucleotide exchange factors (GEFs) and GTPase activator proteins (GAPs) (Buday and Downward, 2008; Vigil et al., 2010; Liu et al., 2017). Figure 1 shows a simple schematic diagram of their function. In this cycle, GAPs
The three best known members are Rho (A, B, C), Rac and Cdc42 (Takai et al., 2001; Shenoy and Lefkowitz, 2011; Reiter et al., 2012; Claiing, 2013). Among them, RhoA, Rac1, and Cdc42 have been studied the most (Schwartz and Shattil, 2000; Rolfe et al., 2005; Grosshans et al., 2006). The Rab family is by far the largest family of the Ras superfamily in humans (Rojas et al., 2012). Proteins of this family participate in vesicle formation, movement and fusion, and vesicular cargo trafficking (Pereira-Leal and Seabra, 2001; Segev, 2001). The Arf family includes 30 proteins and is also involved in vesicle trafficking. Ran is the only member found in the Ran family, which is present in all eukaryotic lineages and involved in nuclear transport (Weis, 2003).

All the proteins have a GTP-binding domain of about 20 kDa, also known as the G-domain (Bourne et al., 1991; Takai et al., 2001). As shown in Figure 3, this domain consists of five α helices (A1–A5), six β-strands (B1–B6) and five polypeptide loops (G1–G5). This domain is highly conserved overall, and especially the loops (Paduch et al., 2001). When bound to GDP, small GTPases are inactive. The two states have similar conformations and can be distinguished by two functional loop regions: switch I (corresponds to the G2 loop) and switch II (corresponds to the G3 loop and part of the A2 helix) (Figure 3) (Jurnak, 1985; Paduch et al., 2001). The G1 loop is located between the B1 strands and A1 helix with the motif X1X2X3GXXXGK (S/T), where X1 is leucine (L), valine (V) or isoleucine (I), and X is any amino acid. The α- and β-phosphate groups can be bound to this motif (Knihtila et al., 2015). The G2 loop, with only one conserved threonine (T), that connects the A1 helix and the B2 strand is responsible for the binding of Mg$^{2+}$ via conserved amino acid residues. The G3 loop is at the N-terminus of the A2 helix with the motif XXXDXXGX. Its main function is to bind Mg$^{2+}$ and the γ-phosphoric acid group of GTP or GDP. The G4 loop containing the motif XXX (G/A) (T/N) KXD and the G5 loop are mainly responsible for the recognition of the guanine base (Figure 4).

To date, 167 small GTPases have been identified in humans (Supplementary Table S1) (Rojas et al., 2012; Liu et al., 2017). We compared the G-domain region of those small GTPases, and found that there exist 5 repeated sequences. After removing 5 repeated amino acid sequences that are identical, the resulting 162 amino acid sequences were analyzed and a sequence-homology based phylogenetic tree (Figure 2) was constructed using the Neighbor-Joining method (Saitou and Nei, 1987). According to sequence and functional similarity, small GTPases can be divided into five main families whose eponymous members are Ras, Rho, Rab, ADP-ribosylation factor (Arf) and Ran (Wennerberg et al., 2005). Ras family members, the first members of the superfamily to be discovered, are signal nodes mediating the responses to various extracellular stimuli and can regulate cell proliferation, differentiation, morphology, and apoptosis by binding to a variety of effector molecules with different catalytic activities to regulate the cytoplasmic signaling network (Karnoub and Weinberg, 2008). The Rho family includes more than 20 proteins. This family is known for its role in actin cytoskeleton remodeling and cell polarity (Fransson et al., 2003; Heo and Meyer, 2003). The three best known members are Rho (A, B, C), Rac and

![Figure 1](https://example.com/f1.png)

**FIGURE 1** | The two state of small GTPases. GDP- and GDP-bound state are regulated by GEFs and GAPs. GEFs stimulate the exchange of GDP for GTP, resulting activation of Ras (“ON”), GAPs promote GTP hydrolysis, and return Ras to GDP-bound state (“OFF”).

Promote GTP hydrolysis, and GEFs stimulate the exchange of GDP for GTP (McCormick, 1998). GDIs can be defined as a class of proteins interacted with small GTPases, which not only prevent exchange (maintaining the small GTPases in an off-state), but also prevent the small GTPase from localizing at the membrane (Cherfils and Zeghouf, 2013). Importantly, these molecular switches affect almost all cellular processes such as gene expression, microtubule organization, cytoskeleton reorganization, and vesicular and nuclear transport (Johnson and Chen, 2012). Small GTPases can also be influenced by post-translational modifications such as phosphorylation or ubiquitination, which can regulate protein stability and subcellular localization (Ahearn et al., 2011).

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![Figure 2](https://example.com/f2.png)

**Figure 2** | The motif X$^X_1$X$^X_2$X$^X_3$GXXXGK (S/T), where X$^X_1$ is leucine (L), valine (V) or isoleucine (I), and X is any amino acid. The α- and β-phosphate groups can be bound to this motif (Knihtila et al., 2015). The G2 loop, with only one conserved threonine (T), that connects the A1 helix and the B2 strand is responsible for the binding of Mg$^{2+}$ via conserved amino acid residues. The G3 loop is at the N-terminus of the A2 helix with the motif XXXDXXGX. Its main function is to bind Mg$^{2+}$ and the γ-phosphoric acid group of GTP or GDP. The G4 loop containing the motif XXX (G/A) (T/N) KXD and the G5 loop are mainly responsible for the recognition of the guanine base (Figure 4). Although the G-domain is conserved in the superfamily, there are also individual difference among the different small GTPase families. For example, in G1 loop, the sixth position G is only conserved in the Rho, Rab, and Arf families. On the other hand, covalent post-translational modification by lipids is another feature of small GTPases. These modifications are essential for facilitating membrane association and subcellular localization, which is critical for their respective biological activities (Hancock, 2003; Prior and Hancock, 2012). The C-terminal cysteine residue of the motif can be prenylated by farnesyltransferase or geranylgeranyltransferase. This modification was observed for most Ras, Rho, and Rab family members despite the different motifs, which is composed of CAAX (C is Cys, A is aliphatic and X is any amino acid) for Ras and Rho family proteins, and CC, CXC, CCX, CCXX, or CCXXX for the Rab family (Cox and Der, 2002; Wennerberg et al., 2005). Some Ras superfamily members without lipid modification, such as Rit, RhoBTB, Miro, and Sar1, can also associate with membranes (Wennerberg et al., 2005). Arf family proteins lack C-terminal lipid modification signals and some members are modified at their N-termini by a myristoylation (Colicelli, 2004). By contrast, Ran does not exhibit
any detectable modification by lipids and binding to membranes (Wennerberg et al., 2005).

Studies of the functions of Ras superfamily proteins in modulating the diverse signaling cascades have established many current fundamental paradigms of signal transduction, mainly based on decades of oncological investigations. The awareness of aberrant Ras-related signaling in the pathogenesis of other human disorders has also risen in recent years. Here we highlight the critical roles of each family of the Ras superfamily in non-neoplastic cerebral diseases (Tables 1–3), which in turn may suggest novel therapeutic targets for developmental diseases and cognitive impairments.

THE Ras FAMILY IN NON-NEOPLASTIC CEREBRAL DISEASES

The Ras Family

As the first described and prototypical members of the small GTPase superfamily, Ras family proteins are almost
universal components of signaling pathways in eukaryotic organisms, including vertebrates, invertebrates, and yeasts (Goitre et al., 2014). Ras genes were first identified as oncogenes, and were named after the Rat Sarcoma gene in the 1970s during the extensive study of acutely transforming retroviruses isolated from mice, rats, and other animals (Cox and Der, 2010). Following years of investigation, the widespread prevalence of Ras mutations in the context of carcinogenesis has now been widely recognized. This has inspired multiple attempts to find Ras inhibitors. However, as for the role of the Ras family in non-neoplastic diseases, we are still at the beginning stage of discovering how the related proteins and their precise mechanisms control and modulate non-oncogenic processes (Johnson and Chen, 2012).

According to their evolutionarily conservation in structural, biochemical, and functional levels, the Ras family is composed of over 36 members, with six major subfamilies: Ras subfamily (H-Ras, K-Ras, N-Ras, etc.),Ral (RaLA, RaLB), Rap (Rap1, Rap2), Rad (Rad, Gem, etc.), Rheb (Rheb1, and Rheb2 or RhebL1) and Rit (Rit1 or Rit2 or Rin, and Drosophila dRic) (Goitre et al., 2014).

Most Ras family proteins are predominantly localized on the intracellular surface of the plasma membrane as a result of C-terminal prenylation (Colicelli, 2004). They can be activated in response to multiple extracellular stimuli in the form of growth factors and small molecules, which thereby transduce signals to the intracellular environment to regulate cytoplasmic signaling networks (Ye and Carew, 2010).

The best-characterized downstream signaling cascade of Ras family proteins is the Mitogen-Activated Protein Kinase (MAPK) cascade, mainly the Extracellular signal-Regulated Kinase 1/2 (ERK) of the MAPK family (Ye and Carew, 2010). Ras family proteins can directly bind to the regulatory domain of Raf (c-Raf or b-Raf) and subsequently phosphorylate and dephosphorylate it at multiple sites for full activation. In turn, activated Raf phosphorylates and activates MAP Kinase or ERK Kinase (MEK), and finally targets transcription factors to induce gene expression (Lang-Carter and Johnson, 1994). Take Rap subfamily members for example. Rap1 can activate ERK by activating b-Raf (expressed predominantly in the brain) and p38MAPK, which implies a pivotal role in synaptic depression (Grewal et al., 2000; Kanda and Watanabe, 2007). Furthermore, Rap2 is involved in the activation of c-Jun N-terminal Kinase (JNK) (Machida et al., 2004). In addition to the Raf–MEK–ERK cascade, other well-known pathways include the phosphatidylinositol 3-kinase (PI3K), RalGEF-Ral, and phospholipase C epsilon (PLCε) pathways (Pulciani et al., 1982; Santos et al., 1984).

The Rit subfamily is composed of two classes, Rit and Rin (Ras like without CAAAX2, Rit2), each containing a well-conserved GTPase core (G1–G5). Distinct patterns of developmental expression for both proteins were found, whereby Rit is widely expressed throughout development, while Rin shows delayed expression limited to later stages of embryonic neuronal development (E14), with highest Rin expression found in the adult brain (Shi et al., 2013; Hamedani et al., 2017). Activated Rit was identified as playing a critical role in the regulation of neuronal morphogenesis, especially enhancing axonal growth, but with the opposite effect on dendritic growth (Lein et al., 2007).

Rin is involved in calcium-mediated processes in cells and binds to calmodulin through a C-terminal binding motif, regulating the Rin-mediated pathway (Hoshino and Nakamura, 2002; Daneshmandpour et al., 2018). Rin has an important role in intracellular signaling and interacts with DAT (dopamine active transporter) in lipid raft microdomains (Navaroli et al., 2011).

The Rheb subfamily (Ras homolog protein enriched in the brain) is a member of the Ras family that is highly conserved among different organisms (Urano et al., 2001; Schoneborn et al., 2018). Two different Rheb genes have been identified in mammalians, RHEB1 (from here on RHEB), and RHEB2 (also as RHEBL1). RHEB is expressed in various human tissues, but RHEB2 is mainly expressed in the brain tissue, such as cerebral cortex, occipital pole, frontal, and temporal lobes (Saito et al., 2005; Schoneborn et al., 2018).

Mammalian target of rapamycin (mTOR) is a serine-threonine kinase that integrates signals to regulate cell growth and metabolism. In the brain, Rheb functions as a key activator of mTORC1, and deletion of RHEB causes decreased cortical thickness and defective myelination (Lee et al., 2015).

RaLA and RaLB are monomeric GTPases belonging to the Ral subclass, and both are expressed in the nervous system (Teodoro et al., 2013). Ral can be activated either by Ras indirectly via a Ral-GEF (Guanine nucleotide Exchange Factor) or by Ca2+/calmodulin binding, and it is inactivated by
PKC phosphorylation of the effector Sec5 (Harvey et al., 2008; Chen et al., 2011). During brain development, it is considered that Ras is involved in the asymmetric division of neuroblasts, neuronal migration in the neocortex, neurite branching, and activity-dependent spine growth (Das et al., 2014). RalA regulates axon initiation in cortical neurons by promoting an interaction between the exocyst protein complex, which is one of its major effectors, and the Par3–Par6–aPKC complex, an evolutionarily conserved master regulator of cell polarity. However, in other cell migration processes, such as tumor metastasis, it seems that RalB may play a more important role than RalA (Zago et al., 2017).

The Rap subfamily is composed of five related proteins, Rap1 (A and B) and Rap2 (A, B, and C), which have overlapping functions and expression patterns (Nakamura et al., 2013; Zhang L. et al., 2018). Similar to other members of the Ras family, Rap proteins work as molecular switches of multiple signal transduction cascades and are linked to several genetic defects related to mental, neurological and psychiatric disorders (Volk et al., 2015). Rap1 has been extensively investigated for its function in integrin-mediated cell adhesion and the regulation of cell–cell junction integrity (Jossin, 2011). A recent study indicates that Rap1 and Rap2 predominantly signal synaptic depression via the lysosomal p38MAPK and the bulk membrane JNK pathway, respectively, regulating different forms of synaptic plasticity (Zhang L. et al., 2018). Especially, Rap1B acts as a core molecule in the signaling network responsible for neuronal polarization (Nakamura et al., 2013).

Diseases Related to the Ras Family
Owing to the Ras family proteins’ essential role in modulating a wide range of cellular processes, several human diseases are caused by the dysregulation or dysfunction of related signaling pathways. These include cancer, developmental-, neurocognitive- and neurodegenerative disorders, as well as metabolic and cardiovascular diseases (Nakhaei-Rad et al., 2018). In this section, we reviewed some Ras family related developmental disorders and neurological diseases.

RASopathies
The RASopathies are the largest known group of rare human developmental disorders that are caused by germline mutations in genes that encode proteins of the RAS/MAPK pathway, resulting in its hyperactivation (Tajan et al., 2018). As mentioned above, the RAS/MAPK pathway is essential for the development of mammalian tissues, controlling a variety of cellular activities, such as cell cycle and growth, differentiation, metabolism and senescence (Slack, 2017). Although this signaling pathway is often summarized as a well-established cascade, there are still many gray areas and multilevel regulations, such as transcriptional control, posttranslational modifications, protein–protein interactions, and crosstalk with other signaling pathways. In this section, we mainly focus on individual symptoms,
phenotypes and most evidenced gene mutations to the RASopathies. Further detailed information on comprehensive functional and pathophysiological consequences could be referred to suggested reviews (Atay and Skotheim, 2017; Simanshu et al., 2017).

The RASopathies include neurofibromatosis type 1 (NF1), Legius syndrome (LS), capillary malformation–arterio-venous malformation syndrome (CM-AVM), Costello syndrome (CS), cardio-facio-cutaneous syndrome (CFC), Noonan syndrome (NS) and Noonan syndrome with multiple lentigines (NS-ML) (Simanshu et al., 2017; Dard et al., 2018). Although RASopathies exhibit unique phenotypes, they share many overlapping clinical characteristics due to the common pathway dysregulation, such as partial facial anomalies, cognitive impairment, and congenital heart defects (Nakhaei-Rad et al., 2018). As a whole, the RASopathies affect approximately 1 per 1,000 live births (Tajan et al., 2018). The initial diagnosis of a RASopathy patient is based on the clinical recognition of phenotypic features, and the clinical diagnosis is then confirmed by molecular genetic tests. To date, with the accumulation of genotype and phenotype correlation data, there are more than 20 gene mutations has been associated with RASopathies. Most mutations causing RASopathies occur at conserved positions within the RAS/MAPK pathway, providing a genetic foundation for their diagnosis and pathophysiology (Simanshu et al., 2017). Table 1 has listed several gene mutations related to small GTPases, especially the Ras family and RASopathies. However, considering the heterogeneity of a given syndrome and the pleiotropic roles during development and homeostasis maintenance, it is still difficult and fragmental to classify the causal genes and mutations involved with the genotype/phenotype correlations based on current progress.

NS was first described by Jacqueline Noonan about 50 years ago, and is also the most frequent RASopathy. Its estimated prevalence is between 1 in 2,000–2,500 newborns (Noonan, 1968; Tajan et al., 2018). It is an autosomal dominant disorder and the most genetically diverse RASopathy, which is clinically characterized by facial dysmorphic features, congenital heart defects, and growth retardation. More than half of patients with NS are identified as having mild to moderate developmental delay/learning disability, notably with social and communication difficulties, attention deficit, and language impairment (Cesarini et al., 2009). Most of the mutations responsible for NS affect familiar components of Ras pathways. The protein tyrosine phosphatase non-receptor type (PTPN11), encoding SHP2, is the first and major NS disease gene, which was confirmed by molecular genetic tests. To date, with the current progress.

NS-ML, formerly known as LEOPARD syndrome, is an autosomal dominant disorder that has a prevalence of fewer than 1 in 100,000 newborns (Sarkozy et al., 2008). However, considering that the phenotype of NS-ML is very close to that of NS, the diagnosis can be more difficult (Sarkozy et al., 2008). Distinctive clinical features for NS-ML are a high prevalence of hearing deficits (20%) and multiple pigmented skin lesions called lentigines, mostly starting at school age (90%) (Sarkozy et al., 2008). Missense mutations in PTPN11 (Legius et al., 1993; Digilio et al., 2006) and rarely in RAF1 (Pandit et al., 2007) and BRAF (Digilio et al., 2006) are associated with NSML. Loss of function mutations in the PTPN11 gene result in reduced SHP2 activity, which is not found in NS (Digilio et al., 2002; Kontaridis et al., 2006). A recent study implied that the Ras-related Akt-mTOR signaling pathway is implicated in NS-ML phenotypes (Marin et al., 2011).

Noonan-like syndrome with loose anagen hair (NSLH), also known as Mazzanti syndrome, is phenotypically close to NS, but patients display distinctive hyperactive behavior and pathognomonic hair anomalies (Gripp et al., 2016). SHOC2 and PPP1CB have been indicated with the onset of the disease (Atay and Skotheim, 2017). NF1, the second-most frequent RASopathy, is an autosomal dominant genetic disorder that was first described in 1882 (Garcia-Romero et al., 2016; Simanshu et al., 2017). The incidence of NF1 is 1 per 2,500–3,000 in newborns, with approximately 50% of NF1 patients inheriting the mutation from a parent (Williams et al., 2009). The characteristic feature used for NF1 diagnosis is the presence of café-au-lait macules. Benign tumors (neurofibromas and optic pathway gliomas), iris Lisch nodules, bone malformations (limb pseudarthrosis), cardiac malformations, brain malformations, seizures, and mild neurocognitive impairment can aid the diagnosis (Huffmeier et al., 2006; Stevenson et al., 2006). NF1 is caused by mutations in the NF1 gene on chromosome 17q11.2, which encodes neurofibromin, a GAP that negatively regulates Ras (Cawthon et al., 1990; Legius et al., 1993). NF1 mutations result in the loss of function of neurofibromin, which in turn reduces Ras GTPase activity and finally increases the levels of active GTP-bound Ras. Studies have suggested that neurofibromin can act on M-Ras, R-Ras, and R-Ras2 (a.k.a. TC21) (Ohba et al., 2000). R-Ras and N-Ras activate PI3Kγ, while M-Ras recruits SHOC2/PP1c to the plasma membrane to regulate SCRIB activity (Rodriguez-Viciana et al., 2004; Young et al., 2013). As a consequence, the loss of neurofibromin may have broader impacts on cells than the activation of H-Ras, N-Ras, and K-Ras proteins themselves (Simanshu et al., 2017).

Legius syndrome is a milder form of neurofibromatosis type 1, which shares phenotypic features with NF1, albeit in less severe form (Tajan et al., 2018). However, the NF1 gene is intact and heterozygous inactivating mutations in the SPRED1 gene on chromosome 15q13.2 occur in LS (Brems et al., 2007).
TABLE 1 | Gene mutations related to Small GTPases (Ras family).

| Gene mutations | Related disease | Proteins | Pathway/mechanism | References |
|----------------|----------------|----------|-------------------|------------|
| PTPN11         | NS             | SHIP2: Protein tyrosine phosphatase | Increased RAS/MAPK | Siegfried et al., 2017 |
| PTPN11         | NS-ML          | SHIP2: Protein tyrosine phosphatase | Increased AKT/mTOR | Tajan et al., 2015 |
| SOS1           | NS             | Son of sevenless homolog 1 | Increased RAS/MAPK, Rac, and Stat3 | Van Trier et al., 2017 |
| RAF1           | NS             | v-Raf-1 murine leukemia viral oncogene homolog 1 | Increased RAS/MAPK | Yin et al., 2017 |
| RAF1           | NS-ML          | v-Raf-1 murine leukemia viral oncogene homolog 1 | Increased RAS/MAPK | | |
| KRAS           | NS             | V-Ki-Ras2 Kirsten rat sarcoma viral oncogene homolog | Increased RAS/MAPK | Tartaglia et al., 2011 |
| KRAS           | CFCS           | Neuroblastoma Ras viral (V-Ras) oncogene homolog | Increased RAS/MAPK | | |
| NRAS           | NS             | Neurofibromin PI3K/mTOR/AKT pathway | Increased RAS/MAPK | Ekvall et al., 2015 |
| SHOC2          | NS             | soc-2 suppressor of clear homolog | SHOC2-MRAS-PP1 complex positively regulates RAF activity | Young et al., 2018 |
| SHOC2          | NS-LAH         | soc-2 suppressor of clear homolog | | |
| BRAF           | NS             | Serine/Threonine-Protein Kinase B-Raf | Increased RAS/MAPK | Tartaglia et al., 2011 |
| BRAF           | CFCS           | Serine/Threonine-Protein Kinase B-Raf | Increased RAS/MAPK | Tartaglia et al., 2011 |
| RIT1           | NS             | Ras-Like Without CAAX 1 | Increased RAS/MAPK | Aoki et al., 2013 |
| RRAS           | NS             | Related Ras viral (R-Ras) Oncogene Homolog | Related Ras Viral (R-Ras) Oncogene Homolog, Increased RAS/MAPK | Fleix et al., 2014 |
| MAP3K8         | NS             | Ras/MARK pathway | Increased RAS/MAPK | Tidyman and Rauen, 2016a |
| MEK1           | CFCS           | MEK 1: Mitogen-activated protein kinase 1 | Increased RAS/MAPK | Denti et al., 2009 |
| NF1            | NF-1           | Neurofibromin | PISK/mTOR/AKT pathway | Arun et al., 2013 |
| SPRED1         | LS             | Sprouty-related EVH1 domain containing protein 1 | Increased RAS/MAPK and JAK2 | Hirata et al., 2016 |
| SPRED2         | OCD            | Sprouty-related EVH1 domain containing protein 2 | Loss of SPRED2 | Ulrich et al., 2018 |
| HRAS           | CS             | Harvey rat sarcoma viral oncogene homolog | Increased RAS/MAPK | Bertola et al., 2017 |
| RIT2 (rs12456492) | Parkinson’s disease | CD33 | rs12456492 polymorphism is associated with increased CD33 expression | Liu et al., 2015 |
| RIT2 (rs12456492) | Essential tremor | – | – | Emamalianzadeh et al., 2017 |
| RIT2 (rs16976358) | Autism spectrum disorder | Regulatory motif of the SOX transcription factor | rs16976358 variant | Hamedani et al., 2017 |
| RIT2 (rs16976358) | Schizophrenia | – | CNV | Rees et al., 2014; Tansay et al., 2016 |
| RIT2 (rs16976358) | Bipolar disorder | – | – | Emamalianzadeh et al., 2017 |
| RIT2 (rs14130047) | Autism spectrum disorder | – | – | Hamedani et al., 2017 |

NS, Noonan syndrome; NS-ML, Noonan syndrome with multiple lentigines; NS-LAH, Noonan-like syndrome disorder with loose anagen hair; NS-LAH, Noonan-like syndrome disorder with loose anagen hair; CS, Costello syndrome; CFCS, Cranio-facio-cutaneous syndrome; LS, Legius syndrome; OCD, Obsessive compulsive disorder; NF-1, Type 1 neurofibromatosis; CNVs, Copy number variations.

SPRED1 functions as a negative regulator of Ras by inhibiting the phosphorylation of Raf (Wakioka et al., 2001). The SPRED1 proteins are essential for the interaction of neurofibromin with Ras at the plasma membrane. It is suggested that SPRED2 and SPRED3 proteins can partially compensate the loss of SPRED1 function (Simanshu et al., 2017). Although SPRED1 binding does not affect neurofibromin’s GAP activity, it nevertheless plays an important role in enabling neurofibromin to downregulate Ras activity at the plasma membrane.

CFCS is a rare autosomal dominant disease with multiple congenital anomalies that affects 1/800,000 newborns (Pierpont et al., 2014). It shares many overlapping features with NS (e.g., heart defects, short stature, and facial features) but is additionally characterized by thick scaly skin, delayed growth and cardiac malformations (Rauen, 2007). Affected individuals frequently have severe neurological disturbances and mental retardation (Yoon et al., 2007). CFCS is caused by heterozygous mutations in BRAF (75% of cases), and less frequently in the MAP2K1 (MEK1), MAP2K2 (MEK2) (20% of cases) and k-ras genes (Rodriguez-Viciana et al., 2006). BRAF is a downstream effector of Ras, and activating BRAF can increase the activation of the MAPK pathway by CRAF (Heidorn et al., 2010).
Costello syndrome is a multiple congenital anomaly syndrome caused by heterozygous activating germline mutations in HRAS. A common and distinctive feature of CS among RASopathies is an increased risk of developing cancers such as rhabdomyosarcomas and neuroblastomas. A recent study has found an increased energy expenditure (EE) in patients with CS, resulting in growth failure (Leoni et al., 2016).

CM-AVM is associated with arteriovenous malformations and fistulas, and is caused by heterozygous inactivating mutations in RASA1 (Eerola et al., 2003). RASA1 encodes p120-RasGAP, which is a negative regulator of the RAS/MAPK signal transduction pathway. RASA1 mutations have also been associated with the related condition known as Parkes Weber syndrome (Banizc et al., 2017).

From the functional perspective, the global relationship for different syndromes could emerged as this: NS and NS-ML are mainly related with activators of the RAS/MAPK cascade (i.e., RAS or RAF activators), but NF and LS are associated to RAS inhibitors. In addition, CS and CFCS mutations hit the backbone of the pathway, while CS being centered on RAS and CFCS on downstream kinases (Atay and Skotheim, 2017).

Future prospective
With the continuous investigation and further understanding of causal mutations and functional analysis of pathophysiological consequences of RASopathies, tremendous advances have been made in the past 30 years. Whereas, given the current fragmentary view, the complexity of RASopathies determined that more issues and challenges lie ahead, such as unidentified causal genes in patients with RASopathies, further functional analyses of the newly discovered mutations, the precise mechanisms underlying the RASopathies (similarities and differences between RASopathies), and the variable expression of a gene mutation (Atay and Skotheim, 2017). In addition, we should take into account of the endocrine and metabolic prospective to interrogate the interactions and contributions of different mutations to the homeostasis imbalance and global phenotype. Moreover, additional factors, such as environmental, age-related and sex-related modifiers, may multifield the difficulty to decipher its pathophysiological process.

Neurological and Psychiatric Disorders
Alzheimer’s disease (AD) is the most common progressive neurodegenerative disorder, affecting more than 30 million people worldwide (Stornetta and Zhu, 2011). The disorder is characterized by early deficits in learning and memory followed by loss of other higher cognitive functions, which is correlated with synaptic depression and then neuronal degeneration (Haass and Selkoe, 2007). It is still unclear that what factors determined the age of onset and how the selective dysfunction of neurons in the brain been affected. A hallmark of AD pathology is the generation of amyloid beta (Aβ) from the amyloid precursor protein (APP) by APP-cleaving enzyme 1 (β-secretase, BACE1) (Schoneborn et al., 2018). Studies showed the underlying mechanism for physiological regulating BACE1 stability and activity in its GTP-bound state was Rheb GTPase, which induced mammalian target of rapamycin (mTOR) activity. Protein levels of BACE1 and Aβ generation are suppressed upon Rheb overexpression (Schoneborn et al., 2018). The interaction of GTP-activated Rheb with BACE1 stimulates its degradation via the proteasomal and lysosomal pathways (Shahani et al., 2014). Recently correlation study implied that the nutrient signaling might regulate cognitive functions in mammals by regulating Rheb–BACE1 and Rheb–mTOR pathways activity, which also orchestrated a potential new therapeutic target for Alzheimer’s-associated memory dysfunction (Shahani et al., 2017).

Parkinson’s disease (PD) is the second most common neurodegenerative disorder following Alzheimer’s disease, affecting 1–2% of the population above 60 years of age (Karimi-Moghadam et al., 2018). Although most PD cases occur sporadically, mutations in several genes, such as SNCA (α-synuclein), PARK2 (parkin), DI-1, PINK1, ATP13A2, VPS35 (vacuolar protein sorting 35), EIF4G1 (eukaryotic initiation factor 4G1) and LRRK2 (leucine-rich repeat kinase 2), have been identified in hereditary PD (Tsika and Moore, 2013). LRRK2 is a large, multifunctional protein with a central catalytic GTPase/kinase core flanked by several protein-binding domains. Seven missense mutations, clustered in the Ras-of-complex (ROC) GTPase domain, C-terminal-of-ROC (COR) and kinase domains, segregate with PD in affected families (Atashrizm et al., 2018; Pfeffer, 2018). Dopaminergic signaling also plays a critical role in the pathogenesis of PD, and dopamine transporter (DAT) serves as a primary mechanism for terminating dopaminergic signaling (Shi et al., 2013). Rit2 (Rit2) was recently identified as a protein that interacts with the DAT C-terminal endocytic domain, implying a role of Rit2 signaling in the regulation of DAT trafficking (Navaroli et al., 2011). In addition, studies from the perspective of immunity have also indicated that Rit2 polymorphisms affect the innate immune system, which in turn is responsible for some PD symptoms (Chan et al., 2016). Recent genome wide association study (GWAS) and meta-analysis results introduced Rit2 as a novel susceptibility locus, in association with decreased Rin expression in the substantia nigra pars compacta (SNc) of PD patients (Bossers et al., 2009; Latourelle et al., 2012; Pankratz et al., 2012). However, the results of RIT2 polymorphisms studies in different populations are controversial, which may be due to genetic context difference and environmental factors (Daneshmandpour et al., 2018). Therefore, further functional study, animal study and larger study with various population samples might give more detailed role of RIT2 in cells and groups in PD pathogenesis.

Huntington’s disease (HD) is a fatal autosomal-dominant neurodegenerative disease caused by CAG repeat expansion in exon 1 of huntingtin, which encodes the protein huntingtin (Htt). HD results in early loss of medium spiny neurons in the striatum, which impairs motor and cognitive functions (MacDonald et al., 1993). In HD, Htt contains an expanded poly-glutamine (poly-Q) tract. Under healthy conditions, Htt promotes signaling through mTORC1 (mammalian target of rapamycin complex 1). In the case of HD, the poly-Q tract potentiates the signaling by promoting the formation of a ternary complex of Htt-Rheb-mTOR, leading to enhanced mTORC1...
activity (Sathasivam et al., 2013). In the striatum, Rhes (Ras homolog enriched in the striatum) serves as a key activator of mTORC1 (Pryor et al., 2014). Knockout of Rhes reduces mTORC1 activity and attenuates the adverse responses of L-DOPA-induced dyskinesia (Subramaniam et al., 2011; Lee et al., 2015). In addition, Rhes facilitates SUMOylation, a process implicated in HD pathogenesis (Subramaniam et al., 2009). Because Rhes is highly expressed in the striatum (Spano et al., 2004), it has been proposed that Rhes-Mutant Htt interactions may underlie the prominent striatal degeneration observed in HD. There is evidence that impaired Rhes/mTORC1 activity is relevant to the notable striatal pathogenesis in HD, which suggests that impaired mTORC1 function may represent a fundamental mechanism underlying the complex disease phenotypes of HD (Lee et al., 2015).

Autism spectrum disorders (ASD) are a continuum of complex neurological disorders interfering with normal social behavior and cognitive development (Hamedani et al., 2017). They are common neurodevelopmental diseases with onset prior to the age of three, affecting almost 1% of individuals worldwide (Liu et al., 2016). Children with ASD often show a large head circumference and develop epilepsy, and nearly half display severe intellectual disability (Stornetta and Zhu, 2011). ASD has a strong but complex genetic component. A recent study identified an increase in RIT1 transcript levels in patients with autism, implying that RIT may represent an ASD susceptibility gene (Garbett et al., 2008). Considering that several factors, such as abnormal assembly of synapses and dendritic spines, contribute to autism’s pathogenesis, the RIT signal pathway that regulates synaptic development and function might be a novel potential therapeutic target (Ebert and Greenberg, 2013).

Schizophrenia is a devastating psychiatric disorder characterized by reality distortion, with onset in late adolescence and unclear etiology (Glessner et al., 2010). Common features are positive symptoms, such as hallucinations, delusions, disorganized speech, and negative symptoms, such as social deficits, lack of motivation, anhedonia, and impaired emotion processing, as well as cognitive deficits with occupational dysfunction (Arajarvi et al., 2005). Previous studies have reported various copy number variations (CNVs) related to schizophrenia (Piluso et al., 2017; Zhuo et al., 2017). Several recent studies have suggested that the rit2 gene might be involved in the pathogenesis of schizophrenia (Glessner et al., 2010). When compared with control subjects, patients with schizophrenia present a significant enrichment of common interstitial deletions (Bouquillon et al., 2011). Among the deleted genes, rit2 was identified as a candidate gene for language delay, mental retardation, and behavioral abnormalities (Bouquillon et al., 2011). Evidence indicates that ret and rit2, both Ras-related genes important for neural crest development, are significantly affected by CNVs (Glessner et al., 2010). Rit2 is involved in the ubiquitin E3 ligase growth factor pathway that affects mitochondrial dysfunction, which is linked with both schizophrenia and autism (Prabakaran et al., 2004).

The protein interactions in the cells are common. Malfunction or alterations in the protein-protein interaction may influence vast biological functions. Selected members of Ras subfamily and their related possible interacting proteins are listed in the Table 2. Specifically for RIT2, evidence suggests that proteins interacting with RIT2 may cause or relate to similar clinical signs or diseases, which implied that RIT2 might be a potential candidate gene underlying several neurological diseases, such as PD, schizophrenia and autism (Daneshmandpour et al., 2018).

Considering the new insight of the role of members of Ras subfamily in neuro-psychiatric disorders and metabolic regulation, substantial novel therapies might be developed or repurposed based on the extensive studies of Ras subfamily signaling in the context of cancer. For example, evidence suggests trametinib, a small molecule inhibitor targets the MEK kinase with high specificity, extends lifespan in Drosophila and protects against the malfunction of genetic induced obesity in mice (Slack et al., 2015).

THE Rho SUBFAMILY IN NON-NEOPLASTIC CEREBRAL DISEASES

In the mid-1980s, Madaule and Axel (1985) serendipitously identified the first Ras homolog in Aplysia sea slugs, and named it Rho. In recent decades, the Rho subfamily of small GTPases has been shown to regulate many aspects of basic cellular processes such as cell polarity, cell movement, cell–cell interaction, cell proliferation and differentiation, cell morphology, secretion, adhesion, gene expression and survival (Watabe-Uchida et al., 2006; Boureux et al., 2007; Cingolani and Goda, 2008; Peru Y Colón de Portugal et al., 2012; Goitre et al., 2014). More than 20 Rho members, which are structured into six subclasses, are found in all eukaryotic cells as a molecular switch for actin cytoskeleton reorganization (Hall, 2012; Narumiya and Thumkeo, 2018). The Rho subfamily of small GTPases plays essential roles from changes in intracellular cytoskeleton dynamics to extracellular message exchange (Zamboni et al., 2018). In particular, Rho GTPases regulate dendritic arborization, spine morphogenesis, growth cone development, and axon guidance (Stankiewicz and Linseman, 2014). The Rho subclass, including RhoA, RhoB, and RhoC, predominantly promotes the formation of actin stress fibers and focal adhesion (Aspenstrom et al., 2004; Fernandez-Sauze et al., 2009). The Rac subclass (Rac1, Rac2, Rac3, and RhoG) promotes actin chain formation during the branching of lamellipodia, and the cell division cycle. 42 GTP-binding protein (Cdc42) subclass (Cdc42, TC10/RhoQ and TCL/Rhoj) mainly controls the formation of actin microspikes and filopodia (Azzarelli et al., 2014; Goitre et al., 2014).

Rho signaling is involved in several cerebral diseases, including intellectual disability (ID), epilepsy, drug addiction, HD, amyotrophic lateral sclerosis (ALS), and AD, and it acts by regulating axonogenesis, neuronal migration and synaptic plasticity (Table 3) (Mendoza-Naranjo et al., 2007; Locke et al., 2009; Zhang Y. et al., 2015; Li et al., 2016; Wang et al., 2017; Zimering, 2018; Costain et al., 2019). Rac1 and Rac3 are associated with intelligence by regulating key cellular functions in the central nervous system (Rejinders et al., 2017; Costain et al., 2019). Moreover, it was confirmed that missense mutations in
| Small GTPase | Interacting proteins | Related diseases/function | Pathway/mechanism | References |
|-------------|----------------------|--------------------------|-------------------|------------|
| Rit2 (Rin)  | NGF                   | Alzheimer's disease      | Increased RAS/MAPK | Besga et al., 2017 |
|             |                      | Huntington's disease     | Increased AKT/mTOR | Chaldakov et al., 2009; Zhang et al., 2013 |
| RIT1        | Noonan syndrome      | Mental retardation, microcephaly, and epilepsy | Increased RAS/MAPK, Rac, and Stat3 | Yaota et al., 2016; Sonmez et al., 2017 |
| TECR        | Non-syndromic mental retardation | Increased RAS/MAPK | Caliskan et al., 2011 |
| NTRK1       | Hereditary sensory and autonomic neuropathy type V | Congenital insensitivity to pain with anhidrosis | Houlden et al., 2001 |
|             | POU4F1                | Autism                   | Copy number variations (CNVs) | Indo, 2001 |
| Rit1 (Rit)  | B-Raf                | Neuronal development and regeneration | Activation of the B-Raf/ERK and p38 MAP kinase cascades | Salyakina et al., 2011 |
| p38 MAPK    |                      | Neurite outgrowth and cell survival | Rit GTPase-p38-MK2-9 kinase survival pathway | Shi and Andres, 2005 |
| MK2         |                      | Cell survival            | MK2 signaling complex | Shi et al., 2013 |
| HSP27       |                      | Cell survival            | p38-MK2-HSP27-4 Akt activation | Shi et al., 2013 |
| Akt         |                      | Cell survival            | RGL3 activation | Shao and Andres, 2000 |
| Rheb        | mTOR                 | Promoting growth, cell cycle progression and inhibition of autophagy | Growth factor-induced mTOR1 activation | Sokolov et al., 2018 |
| TSC complex |                      | Form a complex with Rheb at the lysosomal membranes | Growth factor-induced mTOR1 activation | Lim and Crino, 2013 |
| PLD1        |                      | Rheb binds and activates phospholipase D1 (PLD1) in a GDP-dependent manner | mTOR1 activation | Zheng et al., 2014 |
| GAPDH       |                      | GAPDH regulates mTOR activity by sequestering the Rheb. | Rheb–GAPDH interaction | Lee et al., 2009 |
| FKBP38      |                      | Coordinate membrane targeting of Rheb | Rheb interacts with FKBP38 and prevents its association with mTOR | De Cicco et al., 2018 |
| RASSF1      |                      | Rheb form complex with RASSF1A to coordinate Hippo and TOR signaling | Hippo pathway activator | Nelson and Clark, 2016 |
| NIX         |                      | Rheb interacts with mitochondrial autaphagic receptor Nix and the autophagosomal protein LC3-I/II | Activation of mitophagy | Meisler et al., 2013; Sugiuara et al., 2015 |
| LC3         | Syntenin              | Rho4 protein syntenin preferentially binds to the GDP-bound form of Rheb. | Rheb-syntenin signaling | Sato et al., 2015 |
| CAT         |                      | Rho binds to CAD protein, a multifunctional enzyme required for the synthesis of pyrimidine nucleotides. | CAD binding is more pronounced with Rheb2 than with Rheb1 | Tyagi et al., 2015 |
| PERK        |                      | Rho inhibits protein synthesis by activating the PERK-ElF2α signaling pathway | Phosphorylation of ElF2α and PERK interplay | Shahani et al., 2017 |
| BACE1       | Aging and Alzheimer's disease. | Forebrain Rheb promotes aging-associated cognitive defects | Rheb depletion increased the levels of BACE1 | |

Rac3 cause severe intellectual disability and brain malformations in humans (Costain et al., 2019). Previous studies have shown that X-linked ID is related to mutations in genes that code for regulators of the small-GTPase family such as Rac/Cdc42 guanine nucleotide exchange factor 6 (αPIX), RhoGEF and trio Rho guanine nucleotide exchange factor (TRIO) (Lelieveld et al., 2016; Reijnders et al., 2017; Zamboni et al., 2018).

Rac1 is essential for diverse forms of learning, and contributes to extinction of an established memory during drug withdrawal or alcohol use disorders (Peru Y Colón de Portugal et al., 2012; Wang et al., 2017). A recent study provided evidence that Rac1-dependent GABA-A receptor endocytosis plays a crucial role in the extinction of aversive memories (Wang et al., 2017). Furthermore, Rho signaling is involved in regulating neuronal synaptic plasticity in the nucleus accumbens (NAc) and ventral tegmental area (VTA), which both play crucial roles in the reward circuitry (Deguchi et al., 2016). These actions of Rho-associated kinase (ROCK) signaling might also be related to synaptic
| Small GTPase | Related disease | Pathway/mechanism | References |
|-------------|----------------|------------------|------------|
| Rac3        | A novel neurodevelopmental syndrome | De novo monoallelic missense variants in Rac3, including one recurrent change | Costain et al., 2019 |
| RhoA        | Diabetic Parkinson’s disease or dementia | Accelerated neuron loss via the 5-hydroxytryptamine 2 receptor | Zimering, 2018 |
| Cdc42       | Epileptic-seizures | Regulating synaptic inhibition | Zhang Y. et al., 2015 |
| Rac1        | Fragile X syndrome | Rac1 is necessary for normal spine development and long-term synaptic plasticity | Bongmba et al., 2011 |
| Rac1        | Epilepsy | Patients suffering from temporal lobe epilepsy (TLE) and experimental epileptic rats | Li et al., 2016 |
| RhoB        | Glioblastoma | Cytokine-induced STAT3 activation, activated p53 and p21 | Ma et al., 2015 |
| Rac1 and Cdc42 | Developmental delay, secondary macrocephaly, seizures, and ataxic gait | De novo PAK1 mutations c.392A>G (p.Tyr131Cys) and c.1286A>G (p.Tyr429Cys) | Harms et al., 2018 |
| Rac1        | Drug withdrawal | Rac1-dependent GABAAR endocytosis, synaptic plasticity as well as learning and memory | Wang et al., 2017 |
| Rac1        | Alcohol use disorders | Rac1/Arfaptin/Arf6 pathway | Peru Y Colón de Portugal et al., 2012 |
| RhoA        | Cocaine | Phosphorylated ERM levels and synaptic changes in the NAcc | Kim et al., 2009 |
| Rab7        | Parkinson’s disease | Clearance of α-synuclein aggregates | Saridaki et al., 2018 |
| Rab11       | Parkinson’s disease | Reduces α-synuclein aggregation and toxicity | Chutna et al., 2014 |
| Rab39b      | Parkinson’s disease | Reduce steady-state levels of α-synuclein | Wilson et al., 2014 |
| Rab         | Infantile encephalopathy | Rab GTPase-Activating Protein dysregulates mTOR signaling | Chong et al., 2016 |
| Rab1A       | Alzheimer’s disease | Mediates Golgi dynamics | Mohamed et al., 2017 |
| Rab3A       | Alzheimer’s disease | Localizes in presynaptic vesicles and regulates exocytosis | Udayar et al., 2013 |
| Rab4        | Alzheimer’s disease | Regulates endosomal recycling | Ginsberg et al., 2011 |
| Rab5        | Alzheimer’s disease | Modulates endosomal membrane trafficking, sorting and endosomal fusion | Ginsberg et al., 2010a,b |
| Rab6        | Alzheimer’s disease | Regulates retrograde Golgi-ER trafficking | Scheppe et al., 2007 |
| Rab7A       | Alzheimer’s disease | Controls transport to late endosomes and lysosomes regulates tau secretion | Ginsberg et al., 2011; Rodriguez et al., 2017; Zafar et al., 2017 |
| Rab8        | Alzheimer’s disease | Modulates polarized trafficking | Shimohama et al., 1999; Kametani et al., 2004; Li et al., 2012 |
| Rab10       | Alzheimer’s disease | pRab10-T73, decrease in Aβ42 and Aβ42/Aβ40 ratio | Ridge et al., 2017; Yan et al., 2018 |
| Rab11A/Rab11B | Alzheimer’s disease | Regulates both endocytic and exocytic trafficking pathways | Udayar et al., 2013; Buggia-Prevot et al., 2014; Xu et al., 2015; Zhao et al., 2015 |
| Rab14       | Alzheimer’s disease | Endocytic recycling and Golgi-endosome trafficking | Linford et al., 2012; Prekeris, 2012 |
| Rab17       | Alzheimer’s disease | Involved in phagocytic removal of apoptotic cells | Udayar et al., 2013 |
| Rab24       | Alzheimer’s disease | Involved in autophagy | Ginsberg et al., 2010a |
| Rab27       | Alzheimer’s disease | Regulates exocytosis, endocytosis and phagocytosis | Ginsberg et al., 2011 |
| Rab36       | Alzheimer’s disease | Involved in late endosome and lysosome distribution | Udayar et al., 2013 |
| Rab3a       | Glioma | Increases cyclin D1 expression | Kim et al., 2014 |
| Rab38       | Glioblastomas | Whole genome mRNA expression microarray data on 220 glioma samples from the Chinese glioma genome atlas | Wang and Jiang, 2013 |
| Rab28       | Cone-rod dystrophy | Retinal dystrophies | Roosing et al., 2013 |
| Arf1        | Creutzfeldt-Jakob disease | Arf/Rho/MLC signaling | Zafar et al., 2015 |
| Arf2 and Arf3 | Retina disease | Participate in the trafficking of lipidated membrane-associated proteins and colocalize in the inner segment with UNC119A and PDE3 | Veel et al., 2008a; Zhang H. et al., 2015; Hanke-Gogokhia et al., 2016a; Moshiro et al., 2017 |
| Arf6        | Alcohol use disorders | Rac1/Arfaptin/Arf6 pathway | Peru Y Colón de Portugal et al., 2012 |
| Arf6        | Diabetic retinopathy | Regulates VEGFR2 trafficking and signal transduction | Zhu et al., 2017 |
| Arf6        | ALS | Potential driver pathophysiological events involving endoplasmic reticulum stress and autophagy | Zhai et al., 2015 |
| Arf72A      | Retina disease | Rescues the ninaE(D1)-related membrane accumulation and suppresses ninaE(D1)-triggered retinal degeneration | Lee et al., 2011 |
| Arl2        | Bardet–Biedl syndrome type 3 | Disrupt a threonine residue important for GTP binding and function of several related small GTP-binding proteins | Fan et al., 2004 |
| Ran         | Frontotemporal dementia | Regulates nuclear import via TDP-43 pathway | Ward et al., 2014 |
| Ran         | Alzheimer’s disease | Transcription regulators in the nucleus | Mastroeni et al., 2013 |
| Ran         | Glioblastoma multiforme | The Survivin-Ran complex | Guvenc et al., 2013 |

ALS, amyotrophic lateral sclerosis.
plasticity in the lateral amygdala and prelimbic prefrontal cortex, which were also identified as regulators in reward circuits (Lamprocht et al., 2002; Swanson et al., 2017). Furthermore, these studies have shown that Rac1 plays a role in drug addiction by regulating synaptic plasticity and the neuronal projection network. It has also been observed that cocaine reduces the phosphorylation of Ezrin/Radixin/Moesin proteins (ERM) in the NAc by downregulating RhoA-Rho kinase signaling, which may importantly contribute to the initiation of synaptic changes in this site, leading to drug addiction (Kim et al., 2009).

Cdc42 is a small GTPase of the Rho-subfamily that acts as a multifaceted key regulator of neuronal structure and function (Bustelo et al., 2007; Govek et al., 2011; Zhang Y. et al., 2015). Cdc42 plays an important role in regulating epileptic seizures (Zhang Y. et al., 2015). Cdc42 regulates the availability of presynaptic sites for CaV2.1 calcium channel incorporation (Chen et al., 2003; Frank et al., 2009), and presynaptic activation of Cdc42 can mimic the effects of electrical activity that promotes synaptic maturation and plasticity (Shen et al., 2006). Cdc42 is over-expressed in the human cortex of the temporal lobe and in the hippocampus of intractable epilepsy patients after an anterior temporal lobectomy (Xiao et al., 2007). Zhang Y. et al. (2015) demonstrated the effect of Cdc42 on the function of hippocampal CA1 pyramidal neurons and revealed that blocking Cdc42 decreases the spontaneous action potentials (APs), and increases both the miniature inhibitory postsynaptic current (mIPSC) and evoked inhibitory postsynaptic current (eIPSC) (Zhang Y. et al., 2015).

Although Rho subfamily has gained the most attention for its putative role in numerous neurodegenerative diseases, the precise mechanisms as a therapeutic target remain controversial and uncertain. In PD, Rho signaling pathway is a promising therapeutic target (Labandeira-Garcia et al., 2015). Some studies also suggest that mutations in LRRK2 can lead to a decrease in activation of Rac1 related Rho signaling, which causes disassembly of actin filaments leading to modulate cytoskeletal outgrowth and vesicular dynamics, including autophagy (Boon et al., 2014). These functions likely impact modulation of α-synuclein aggregation and associated toxicity in the pathophysiology of PD (Konno et al., 2012). A previous study revealed that ROCK inhibition protects against neuronal death induced by neurotoxins (Borrero et al., 2014). ROCK regulation may provide a new neuroprotective strategy for neurodegenerative diseases, and it has to be settled urgently to develop more potent and selective ROCK regulators.

THE Rab SUBFAMILY IN NON-NEOPLASTIC CEREBRAL DISEASES

The Rab subfamily, which comprises more than 60 members, is currently the largest branch of the Ras superfamily of small GTPases (Wennerberg et al., 2005; Diekman et al., 2011). This protein family is primarily related to various aspects of membrane and protein traffic in the endocytic and secretory pathways (Wennerberg et al., 2005; Cherfils and Zoghbi, 2013; Goitre et al., 2014; Gao et al., 2018). Therefore, dysregulation of Rab GTPases may lead to the pathogenesis of some diseases (Table 3). Many neurodegenerative diseases are characterized by dysfunction of membrane and protein traffic in neurons (Zhang X. et al., 2018). The Rab subfamily has also been related to neurodegenerative disorders such as Alzheimer’s disease and PD (Wilson et al., 2014; Saridaki et al., 2018; Yan et al., 2018). Previous studies have shown that Rab3A, Rab6, Rab8A/Rab8, Rab23, and Rab27b are highly expressed in the brain and participate in synaptic vesicle exocytosis, postsynaptic glutamate receptor dynamics, neurite growth and neural development (Takamori et al., 2006; Ng and Tang, 2008; Uno et al., 2016). Rab3 is the most abundant Rab protein in the brain. It is localized in synaptic vesicles and participates in their fusion and neurotransmitter release (Ng and Tang, 2008; Shin, 2014).

Alzheimer’s disease is clinically characterized by progressive cognitive impairment and memory loss (Bejanin et al., 2017). Two classical pathological features of AD are aberrant phosphorylated forms of tau protein and pathologically generated Aβ peptides (Lee et al., 2001; Alavi Naini and Soussy-Yanicostas, 2015; Bejanin et al., 2017; Bourdenx et al., 2017; Sun et al., 2018). Rab GTPases are implicated in multiple pathological mechanisms, including Aβ production and accumulation in AD (Li, 2011; Ridge et al., 2017; Rodriguez et al., 2017; Yan et al., 2018). Rab1B was found to play a key role in APP trafficking from the ER to the Golgi (Dugan et al., 1995). A study has shown that downregulation of Rab1B blocked APP transport in the ER/Golgi and significantly inhibited Aβ secretion (Dugan et al., 1995). Upregulation of either the early endosome protein Rab5 or the late endosome protein Rab7 increased Aβ trafficking from the cytoplasm to the lysosomes (Li et al., 2012). Previous post mortem studies have shown that the levels of Rab7A are elevated in the brains of AD model mice. Furthermore, some recent studies have shown that Rab7A may regulate tau secretion and tangle propagation in AD (Rodriguez et al., 2017; Zafar et al., 2017). Moreover, Rab11A-positive recycling vesicles accelerated cellular Aβ accumulation (Li et al., 2012).

A large amount of literature has reported the importance of the interaction between Rab GTPases and LRRK2 in PD (Steger et al., 2016; Alessi and Sammler, 2018; Eguchi et al., 2018; Jeong et al., 2018; Madero-Perez et al., 2018; Mir et al., 2018; Pfeffer, 2018). It has been reported that autosomal dominant missense mutations within the LRRK2 gene account for 1–2% of all cases of PD (Paisan-Ruiz et al., 2013). Similarly, variations at the LRRK2 locus also mildly increase the risk for idiopathic PD (Paisan-Ruiz et al., 2013; Domingo and Klein, 2018). A previous study verified that LRRK2 phosphorylates a subgroup of Rab GTPases which includes Rab7, Rab8A, and Rab10, and plays a crucial role in membrane and protein traffic (Gomez-Suaga et al., 2014; Roosen and Cookson, 2016; Steger et al., 2016, 2017). Consistently with the importance of LRRK2 for PD, Rab subfamily members can be seen as regulators of membrane trafficking. Furthermore, Rab phosphorylation was found to be altered in vivo in all the related pathogenic processes (Steger et al., 2016, 2017). Some reports showed that Rab35 and Rab39B may be implied in the pathogenesis of PD (Chiu et al., 2016; Lin et al., 2017). There is increasing evidence that
mutations in Rab29 or Rab39B are related to the impairment of membrane trafficking relevant for PD (Ben-David and Tu, 2015; Domingo and Klein, 2018; Purlyte et al., 2018).

Hearing loss often results in plastic changes in the central auditory pathways, which are also related to members of the Rab family of small GTPase (Dong et al., 2010; Mulders et al., 2014). Gene expression of Rab3A and Rab3GAP1 was found to be decreased in the parafolliculus after acoustic or mechanical cochlear trauma (Dong et al., 2010; Mulders et al., 2014). Moreover, early modulation of Rab GTPase gene expression in the parafolliculus may affect auditory processing by regulating the release of neurotransmitters (Mulders et al., 2014).

Cone-rod dystrophy (CRD) is an inherited retinal dystrophy that belongs to the group of pigmentary retinopathies. It is characterized by primary loss of cone photoreceptors and subsequent or simultaneous loss of rod photoreceptors (Hamel, 2007; Roosing et al., 2013). A previous study has shown that mutations in Rab28 are associated with autosomal-recessive cone-rod dystrophy (Roosing et al., 2013). Rab28 is located in the basal body and ciliary rootlet, where it plays a crucial role in ciliary transport. Other studies have shown that primary ciliogenesis is associated with Rab3A, Rab6A, Rab8, and Rab11, which play an indirect role in rhodopsin transport from the photoreceptors’ inner to the outer segments through the connecting cilium (Moritz et al., 2001; Satoh et al., 2005; Knodler et al., 2010).

THE Arf SUBFAMILY IN NON-NEOPLASTIC CEREBRAL DISEASES

Arf GTPases are a subfamily of proteins in the Ras superfamily that were identified as cargo displacement factors (Ismail et al., 2011). The roles of Arf GTPases include protein trafficking, lipid metabolism and trafficking, as well as actin remodeling in eukaryotic cells via their regulated GTP cycle (D’Souza-Schorey and Chavrier, 2006; Jackson and Bouvet, 2014). According to sequence homology, there are four main classes of Arf proteins in mammals, namely Class I (Arl1–3), Class II (Arl4–5), Class III (Arl6), and unclassified members (Rojas et al., 2012; Jackson and Bouvet, 2014). Arfl is the first member of this small GTPase subfamily, which is viewed as key regulators of eukaryotic cell organization (Kahn and Gilman, 1986; Jackson and Bouvet, 2014). Mutations in Arfl have been shown to be related to autosomal recessive periventricular heterotopia, a disorder that leads to severe malformation of the cerebral cortex (Sheen et al., 2004).

In the last two decades, a series of cerebral diseases associated with Arf GTPases have been studied (Table 3). Previous studies have shown that many Arf-regulated ER–Golgi trafficking processes are defective in ALS (Saxena et al., 2009; Wang et al., 2011; Zhai et al., 2015; Atkin et al., 2017). Moreover, a study has shown that regulation of Arf signaling reverses mutant protein toxicity in ALS by decreasing ER stress and stimulating various types of autophagy in cell lines and animal models (Zhai et al., 2015). Recent studies have shown that Arf proteins which belong to Arf GTPases are associated with retinitis pigmentosa (Veltel et al., 2008a; Zhang H. et al., 2015; Hanke-Gogkhhia et al., 2016b). In the pathogenetic process of retinitis pigmentosa, Arl2/Arl3 signaling plays important roles in photoreceptor function by regulating lipid-modified membrane-associated proteins (Hanke-Gogkhhia et al., 2016b). The formation of a ternary complex between Arl3, its cognate GAP RP2 and its retinal effector HRG4 is also of great importance for photoreceptor function (Veltel et al., 2008b). In a rodent model, regulating the activities of Arl3 GAP can reduce the severity of photoreceptor disease (Zhang H. et al., 2015).

THE Ran SUBFAMILY AND UNCLASSIFIED Ras SUPERFAMILY MEMBERS IN NON-NEOPLASTIC CEREBRAL DISEASES

Ran (Ras-related Nuclear protein) is generally encoded by a single ortholog in eukaryotes (Reiner and Lundquist, 2018). The classic function of Ran is to regulate the cycle of nuclear import and export (Reiner and Lundquist, 2018). There are few literature reports on the relationship between Ran and cerebral diseases (Table 3). A study indicated that the expression of Ran is reduced in AD, and Ran is a pivotal molecule in nucleocytoplasmic transport in AD pathophysiology (Mastroeni et al., 2013).

Ran also plays crucial roles in frontotemporal lobe degeneration (FTLD) by regulating TDP-43 induced retinal neurodegeneration (Ward et al., 2014). FTLD comprises a group of disorders, and is clinically characterized by behavioral and personality changes, language impairment, as well as deficits in executive functioning, and is pathologically associated with degeneration of frontal and temporal lobes (Morris et al., 2012; Pottier et al., 2016). The expression of Ran is found to be reduced by nuclear depletion of TDP-43 in a Grn-KO induced rodent model of retinal neuronal loss (Ward et al., 2014). Retinal neurodegeneration as a new phenotype involves the reciprocal loss of Ran in progranulin-deficient FTLD via an underlying mechanism related to nuclear TDP-43 (Ward et al., 2014). There are also some unclassified members in the Ras superfamily of small GTPases (Rojas et al., 2012), and these also play vital roles in cerebral diseases. Gispert et al. (2015) studied synucleinopathy-induced expression changes in the mouse brain and identified 49 midbrain/brainstem-specific transcriptional dysregulations, including Rab2A downregulation. Mitochondrial Rho GTPase 1 (MIRO1), which is encoded by the rhoT1 gene (Fransson et al., 2003; Tada et al., 2016; Lahiri and Kliomsky, 2017), is involved in mitochondrial homeostasis and apoptosis, as well as PD and cancer (Anvret et al., 2012; Jiang et al., 2012; Schwarz, 2013; Sheng, 2014; Van Der Merwe et al., 2015; Lahiri and Kliomsky, 2017). A recent study showed that MIRO1 is a potential adaptor for microtubule based peroxisome motility in mammalian cells (Castro et al., 2018). Another study has revealed that Rab20 is
related to a genetic mechanism of longitudinal cognitive changes during the transition period from mild cognitive impairment to AD (Lee et al., 2017). Liang et al. (2012) found that Rab20 is substantially upregulated during the acute phase of brain inflammation, and also plays crucial roles in the subsequent inflammatory responses in the brain.

CONCLUSION

Knowledge about the roles of the Ras superfamily of small GTPases in cerebral diseases has considerably grown in the past 30 years. Currently, many research teams all over the world are also trying to identify novel small GTPases, which can be viewed as new regulators and effectors that control the crucial structure and biological functions affected by cerebral diseases. In particular, these important small GTPases have improved the development and applications of cellular and animal disease models. In this review, we mainly discussed how Ras-superfamily GTPases contribute to a range of human cerebral diseases as specific effectors in a series of complex mechanisms. Finally, a helpful summary of all described small GTPases from the Ras superfamily that play a role in cerebral diseases is shown schematically in Table 1–3. Therefore, seeking treatment solutions for the related diseases by identifying the as-yet unknown physiological or pathological functions of more than 167 Ras superfamily members will open new research directions and fields in the following decades.

AUTHOR CONTRIBUTIONS

X-LW and YW designed the study. LQ and CP collected, analyzed data, and wrote the manuscript. S-MH and BL interpreted the data and revised the manuscript. YW edited and polished the manuscript. G-DG and X-LW finalized the manuscript. All authors critically reviewed content and approved final version for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnmol.2019.00121/full#supplementary-material

TABLE S1 | G-domin regions of 167 small GTPases found in humans.
Digilio, M. C., Conti, E., Sarkozy, A., Mingarelli, R., Dottorini, T., Marino, B., et al. (2002). Grouping of multiple-lentigines/LEOPARD and Noonan syndromes on the PTPN11 gene. Am. J. Hum. Genet. 71, 389–394. doi: 10.1086/341528

Digilio, M. C., Sarkozy, A., De Zoarzi, A., Pasolli, G., Limongelli, G., Mingarelli, R., et al. (2006). LEOPARD syndrome: clinical diagnosis in the first year of life. Am. J. Med. Genet. B Neuropsychiatr. Genet. 140, 740–746. doi: 10.1002/ajmg.b.31356

Domingo, A., and Klein, C. (2018). Genetics of Parkinson disease. Handb. Clin. Neurol. 147, 211–227.

Dong, S., Mulders, W. H., Rodger, J., Woo, S., and Robertson, D. (2010). Acoustic trauma evokes hyperactivity and changes in gene expression in guinea-pig auditory brainstem. Eur. J. Neurosci. 31, 1616–1628.

D’ouza-Schorey, C., and Chavrier, P. (2006). ARF proteins: roles in membrane traffic and beyond. Nat. Rev. Mol. Cell Biol. 7, 347–358. doi: 10.1038/nrm1910

Dugan, J. M., Dewit, C., Mcconlogue, L., and Maltese, W. A. (1995). The Ras-related GTP-binding protein, Rab11B, regulates early steps in exocytic transport and processing of the beta-amyloid precursor protein. J. Biol. Chem. 270, 10982–10989. doi: 10.1074/jbc.270.18.10982

Ebert, D. H., and Greenberg, M. E. (2013). Activity-dependent neuronal signalling and autism spectrum disorder. Nature 493, 327–337. doi: 10.1038/nature11860

Eerola, I., Boon, L. M., Mulliken, J. B., Burrows, P. E., Dompmartin, A., Watanabe, T., Eguchi, T., Kuwahara, T., Sakurai, M., Komori, T., Fujimoto, T., Ito, G., et al. (2010a). Microarray analysis of hippocampal CA1 neurons implicates early endosomal dysfunction during Alzheimer’s disease progression. Biol. Psychiatry 68, 885–893. doi: 10.1016/j.biopsych.2010.05.030

Gibson, S. D., Mufson, E. J., Counts, S. E., Wu, J., Allred, M. J., Nixon, R. A., et al. (2010b). Regional selectivity of rab8 and rab7 protein upregulation in mild cognitive impairment and Alzheimer’s disease. J. Alzheimers Dis. 22, 631–639. doi: 10.3233/jad-2010-101080

Gibson, S. D., Mufson, E. J., Allred, M. J., Counts, S. E., Wu, J., Nixon, R. A., et al. (2011). Upregulation of select Rab GTPases in cholinergic basal forebrain neurons in mild cognitive impairment and Alzheimer’s disease. J. Chem. Neuroanat. 42, 102–110. doi: 10.1016/j.jchemneu.2011.05.012

Gispert, S., Kurz, A., Brehm, N., Rau, K., Walter, M., Riess, O., et al. (2015). Complexin-1 and Foxp1 expression changes are novel brain effects of alpha-synuclein pathology. Mol. Neurobiol. 52, 57–63. doi: 10.1007/s12035-014-8844-0

Glessner, J. T., Reilly, M. P., Kim, C. E., Takahashi, N., Albano, A., Hou, C., et al. (2010). Strong synaptic transmission impact by copy number variations in schizophrenia. Proc. Natl. Acad. Sci. U.S.A. 107, 10584–10589.

Goitre, L., Trapani, E., Trabalzini, L., and Retta, S. F. (2014). The Ras superfamily of small GTPases: the unlocked secrets. Methods Mol. Biol. 1120, 1–18. doi: 10.1007/978-1-62703-791-4_1

Gomez-Suaga, P., Rivero-Rios, P., Fdez, E., Blanca Ramirez, M., Ferrer, I., Aiastui, A., et al. (2014). LRRK2 delays degradative receptor trafficking by impeding late endosomal budding through decreasing Rab7 activity. Hum. Mol. Genet. 23, 6779–6796. doi: 10.1093/hmg/ddu395

Govek, E. E., Hatten, M. E., and Van Aelst, L. (2011). The role of Rho GTPase proteins in CNS neuronal migration. Dev. Neurobiol. 71, 528–553. doi: 10.1002/dneu.20850

Grewal, S. S., Horgan, A. M., York, R. D., Withers, G. S., Banker, G. A., and Stork, P. J. (2000). Neuronal calcium activates a Rap1 and B-Raf signaling pathway via the cyclic adenosine monophosphate-dependent protein kinase. J. Biol. Chem. 275, 3732–3738. doi: 10.1074/jbc.275.3.3722

Gripp, K. W., Aldinger, K. A., Bennett, J. T., Baker, L., Tusi, J., Powell-Hamilton, N., et al. (2016). Novel rasopathy caused by recurrent de novo missense mutations in PTP1C closely resembles Noonan syndrome with loose anagen hair. Am. J. Med. Genet. A 170, 2337–2347. doi: 10.1002/ajmg.a.37781

Grosshans, B. L., Ortiz, D., and Novick, P. (2006). Rabs and their effectors: achieving specificity in membrane traffic. Proc. Natl. Acad. Sci. U.S.A. 103, 11821–11827. doi: 10.1073/pnas.0601617103

Guvcenc, H., Pavlyukov, M. S., Joshi, K., Hurt, B., Banasavadi-Siddegowda, Y. K., Mao, P., et al. (2013). Impairment of glioma stem cell survival and growth by a novel inhibitor for Survivin-Ran protein complex. Clin. Cancer Res. 19, 631–642. doi: 10.1158/0878-0732.crr-12-0647

Haas, C., and Selkoe, D. J. (2007). Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer’s amyloid beta-peptide. Nat. Rev. Mol. Cell Biol. 8, 101–112. doi: 10.1038/nrm2101

Hall, A. (2012). Rho family GTPases. Biochem. Soc. Trans. 40, 1378–1382.

Hamedani, S. Y., Gharesouran, J., Noroozi, R., Sayad, A., Omrani, M. D., Mir, A., et al. (2017). RIT2 polymorphisms: is there a differential binding proteins causes Bardet-Biedl syndrome. Nat. Genet. 49, 1240–1249. doi: 10.1038/ng.33987

Hans, C., and Selkoe, D. J. (2007). Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer’s amyloid beta-peptide. Nat. Rev. Mol. Cell Biol. 8, 101–112. doi: 10.1038/nrm2101

Harm, F. L., Kloth, K., Bley, A., Denecke, J., Santer, R., Lessel, D., et al. (2016). Activating mutations in Rap1 and B-Raf signaling pathway via the cyclic adenosine monophosphate-dependent protein kinase. J. Biol. Chem. 275, 3732–3738. doi: 10.1074/jbc.275.3.3722

Hancock, J. F. (2003). Ras proteins: different signals from different locations. J. Biol. Chem. 278, 40,1378–1382. doi: 10.1038/nrm2101

Hanke-Gogokhia, C., Zhang, H., Frederick, J. M., and Baehr, W. (2016a). Arf-like protein 3 (ARL3) regulates protein trafficking and cilogenesis in mouse photoreceptors. J. Biol. Chem. 291, 7142–7155. doi: 10.1074/jbc.m115.710954

Hanke-Gogokhia, C., Zhang, H., Frederick, J. M., and Baehr, W. (2016b). The function of Arf-like proteins ARL2 and ARL3 in photoreceptors. Adv. Exp. Med. Biol. 854, 655–661. doi: 10.1007/978-3-319-17121-0_87

Harms, F. L., Kloth, K., Bley, A., Denecke, J., Santer, R., Lessel, D., et al. (2018). Activating mutations in PAK1, encoding p21-activated kinase 1, cause a neurodevelopmental disorder. Am. J. Hum. Genet. 103, 579–591. doi: 10.1016/j.ajhg.2018.09.005

Harvey, C. D., Yasuda, R., Zhong, H., and Svoboda, K. (2008). The spread of the Ras activity triggered by activation of a single dendritic spine. Science 321, 136–140. doi: 10.1126/science.1159675
Heidorn, S. J., Milagre, C., Whitaker, S., Nourry, A., Niculescu-Duvas, I., Dhomen, N., et al. (2010). Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. Cell 140, 209–221. doi: 10.1016/j.cell.2009.12.040

Heo, W. D., and Meyer, T. (2003). Switch-of-function mutants based on morphology classification of Ras superfamily small GTPases. Cell 113, 315–328. doi: 10.1016/S0092-8674(03)03155-5

Hirata, Y., Brems, H., Suzuki, M., Kanamori, M., Okada, M., Morita, R., et al. (2016). Interaction between a domain of the negative regulator of the Ras-ERK pathway, SPRED1 protein, and the GTAPase-activated protein-related domain of neurofibromin is implicated in lefebvre syndrome and neurofibromatosis type I. J. Biol. Chem. 291, 3124–3134. doi: 10.1074/jbc.m115.703710

Hoshino, M., and Nakamura, S. (2002). The Ras-like small GTP-binding protein Rin is activated by growth factor stimulation. Biochem. Biophys. Res. Commun. 295, 651–656. doi: 10.1006/bbrc.2001.0731-3

Houlden, H., King, R. H., Hashemi-Nejad, A., Wood, N. W., Mathias, C. J., Reilly, M., et al. (2001). A novel TRK A (NTRK1) mutation associated with hereditary sensory and autonomic neuropathy type V. Ann. Neurol. 49, 521–525. doi: 10.1002/ana.103

Huffmeier, U., Zenker, M., Hoyer, F., Kahl, S., and Rauch, A. (2006). A variable negative, not activating, effects. J. Biol. Chem. 281, 6785–6792. doi: 10.1074/jbc.m115.79680

Knodler, A., Swanson, K. D., Barford, D., and Neel, B. G. (2006). PTPN11 (Shp2) mutations in LEOPARD syndrome have dominant negative, not activating, effects. J. Biol. Chem. 281, 6785–6792. doi: 10.1074/jbc.m115.79680

Kohno, M., Hasegawa, T., Baba, T., Miura, E., Sugeno, N., Kikuchi, A., et al. (2012). Suppression of dynamin GTAPase decreases alpha-synuclein uptake by neuronal and oligodendroglial cells: a potent therapeutic target for synucleinopathy. Mol. Neurodegener. 7:38. doi: 10.1186/1750-1326-7-8

Kontaridis, M. I., Chen, Y. H., David, F. S., Barford, D., and Neel, B. G. (2006). PTPN11 (Shp2) mutations in LEOPARD syndrome have dominant negative, not activating, effects. J. Biol. Chem. 281, 6785–6792. doi: 10.1074/jbc.m115.79680

Kohno, M., Hasegawa, T., Baba, T., Miura, E., Sugeno, N., Kikuchi, A., et al. (2012). Suppression of dynamin GTAPase decreases alpha-synuclein uptake by neuronal and oligodendroglial cells: a potent therapeutic target for synucleinopathy. Mol. Neurodegener. 7:38. doi: 10.1186/1750-1326-7-8

Kohno, M., Hasegawa, T., Baba, T., Miura, E., Sugeno, N., Kikuchi, A., et al. (2012). Suppression of dynamin GTAPase decreases alpha-synuclein uptake by neuronal and oligodendroglial cells: a potent therapeutic target for synucleinopathy. Mol. Neurodegener. 7:38. doi: 10.1186/1750-1326-7-8

Kohno, M., Hasegawa, T., Baba, T., Miura, E., Sugeno, N., Kikuchi, A., et al. (2012). Suppression of dynamin GTAPase decreases alpha-synuclein uptake by neuronal and oligodendroglial cells: a potent therapeutic target for synucleinopathy. Mol. Neurodegener. 7:38. doi: 10.1186/1750-1326-7-8
degradation by apolipoprotein E isoforms. J. Biol. Chem. 287, 44593–44601. doi: 10.1074/jbc.m112.420224

Li, J., Xing, H., Jiang, G., Su, Z., Wu, Y., Zhang, Y., et al. (2016). Increased expression of Rac1 in epilepsy patients and animal models. Neurochem. Res. 41, 836–843. doi: 10.1007/s11064-015-1759-y

Liang, Y., Lin, S., Zou, L., Zhou, H., Zhang, J., Su, B., et al. (2012). Expression profiling of Rab GTPases reveals the involvement of Rab20 and Rab32 in acute brain inflammation in mice. Neurosci. Lett. 527, 110–114. doi: 10.1016/j.neulet.2012.08.039

Lim, K. C., and Crino, P. B. (2013). Focal malformations of cortical development: new vistas for molecular pathogenesis. Neuroscience 252, 262–276. doi: 10.1016/j.neuroscience.2013.07.037

Lin, H. H., Wu, R. M., Lin, H. I., Chen, M. L., Tai, C. H., and Lin, C. H. (2017). Lack of RAB39B mutations in early-onset and familial Parkinson’s disease in a Taiwanese population. Neurobiol. Aging 50, 169.e3–169.e4. doi: 10.1016/j.neurobiolaging.2016.10.021

Linford, A., Yoshimura, S., Nunes Bastos, R., Langemeyer, L., Gerondopoulos, A., Moshiri, A., Humpal, D., Leonard, B. C., Imai, D. M., Tham, A., Bower, L., et al. (2017). Arap1 deficiency causes photoreceptor degeneration in mice. Invest. Ophthalmol. Vis. Sci. 58, 1709–1718.

Mulders, W. H., Rodger, I., Yates, C. G., and Robertson, D. (2014). Modulation of gene expression in guinea pig parafollicular cells after induction of hearing loss. F1000Res. 3:63.

Nakamura, T., Yasuda, N., Nagai, H., Koinuma, S., Morishita, S., Goto, A., et al. (2013). Longest neurite-specific activation of Rap1B in hippocampal neurons contributes to polarity formation through RaLa and Nore1A in addition to P13-kinase. Genes Cells 18, 1020–1031. doi: 10.1111/gtc.12097

Nakhaei-Rad, S., Haghibhi, F., Nouri, P., Rezaei Adariani, S., Lissy, J., Kazemein Jasemi, N. S., et al. (2018). Structural fingerprints, interactions, and signaling networks of RAS family proteins beyond RAS isoforms. Crit. Rev. Biochem. Mol. Biol. 53, 150–156. doi: 10.1080/10409238.2018.1431605

Narumiya, S., and Thumkeo, D. (2018). Rho signaling research: history, current status and future directions. FEBS Lett. 592, 1763–1776. doi: 10.1016/j.febslet.2018.03.1087

Navaroli, D. M., Stevens, Z. H., Uzelac, Z., Gabriel, L., King, M. I., Lifshitz, L. M., et al. (2011). The plasma membrane-associated GTase Rin interacts with the dopamine transporter and is required for protein kinase C-regulated dopamine transporter trafficking. J. Neurosci. 31, 13758–13770. doi: 10.1523/jneurosci.2649-11.2011

Nelson, N., and Clark, G. I. (2016). Rheb may complex with RASSF1A to coordinate Hippo and TOR signaling. Oncotarget 7, 33821–33831.

Ng, E. L., and Tang, B. L. (2008). Rab GTases and their roles in brain neurons and glia. Brain Res. Rev. 58, 236–246. doi: 10.1016/j.brainresrev.2008.04.006

Noonan, J. A. (1968). Hypertelorism with Turner phenotype. A new syndrome with cardiac and glial anomalies. J. Cell Sci. 4, 279–288. doi: 10.1242/jcs.03323

Ohta, Y., Mochizuki, N., Yasuda, N., Nagai, H., Koinuma, S., Morishita, S., Goto, A., et al. (2013). Longest neurite-specific activation of Rap1B in hippocampal neurons contributes to polarity formation through RaLa and Nore1A in addition to P13-kinase. Genes Cells 18, 1020–1031. doi: 10.1111/gtc.12097

Ohba, Y., Mochizuki, N., Yamashita, S., Chan, A. M., Schrader, J. W., Hattori, S., Morishita, S., et al. (2011). Regulatory proteins of R-Ras, TC21/R-Ras2, and M-Ras/R-Ras3. J. Biol. Chem. 276, 340–349. doi: 10.1016/j.jbc.2010.07.016

Parvez, K., Sultana, R., Ahmad, I., Bhat, R. A., Masood, A., et al. (2012). Rho regulates mitophagy induced by mitochondrial energetic status. Cell Metab. 17, 719–730. doi: 10.1016/j.cmet.2013.03.014

Mendoza-Narango, A., Gonzalez-Billaut, C., and Maccioni, R. B. (2007). Abetal-42 stimuli activate plasticity in hippocampal neurons through Rac1 and Cdc42. J. Cell Sci. 120, 279–288. doi: 10.1242/jcs.03323
management guidelines. *Pediatrics* 134, e1149–e1162. doi: 10.1542/peds.2013-3189

Piluso, G., Monteleone, P., Galderisi, S., Giugliano, T., Bertolino, A., Rocca, P., et al. (2017). Assessment of de novo copy-number variations in Italian patients with schizophrenia: detection of putative mutations involving regulatory enhancer elements. *World J. Psychiatry* 20, 126–136. doi: 10.1016/j.wjp.2017.1395072

Pottie, C., Ravenscroft, T. A., Sanchez-Contreras, M., and Rademakers, R. (2016). Genetics of FTLD: overview and what else we can expect from genetic studies. *J. Neurochem.* 138(Suppl. 1), 32–53. doi: 10.1111/jn.13622

Prabakaran, S., Swatton, J. E., Ryan, M. M., Huffaker, S. J., Huang, J. T., Griffin, J. L., et al. (2004). Mitochondrial dysfunction in schizophrenia: evidence for compromised brain metabolism and oxidative stress. *Mol. Psychiatry* 9, 684–697, 643.

Préreis, R. (2012). The art of ‘cut and run’: the role of Rab14 GTPase in regulating N-cadherin shedding and cell motility. *Dev. Cell* 22, 909–910. doi: 10.1016/j.devcel.2012.05.002

Prior, I. A., and Hancock, J. F. (2012). Ras trafficking, localization and compartmentalized signalling. *Semin. Cell Dev. Biol.* 23, 145–153. doi: 10.1016/j.semcdb.2011.09.002

Pryor, W. M., Biagioli, M., Shani, N., Swarnkar, S., Huang, W. C., Page, D. T., et al. (2014). Huntingtonin promotes mTORC1 signaling in the pathogenesis of Huntington’s disease. *Sci. Signal.* 7:ra103. doi: 10.1126/scisignal.2005633

Pulciani, S., Santos, E., Lauver, A. V., Long, L. K., Aaronson, S. A., and Barbacid, M. (1982). Oncogenes in solid human tumours. *Nature* 300, 539–542. doi: 10.1038/300539a0

Purlye, E., Dhekne, H. S., Haran, A. R., Gomez, R., Lis, P., Wightman, M., et al. (2018). Rab29 activation of the Parkinson’s disease-associated LRRK2 kinase. *EMBO J.* 37, 1–18. doi: 10.15252/embj.201798089

Rauen, K. A. (2007). HRAS and the Costello syndrome. *Clin. Genet.* 71, 101–108. doi: 10.1111/j.1399-0004.2007.00473.x

Rees, E., Walters, J. T., Chambert, K. D., O’Dushlaine, C., Szatkiewicz, J., Richards, A. L., et al. (2014). CNV analysis in a large schizophrenia sample implicates deletions at 16p12.1 and SLCA1 and duplications at 1p36.3 and CGNL1. *Hum. Mol. Genet.* 23, 1669–1676. doi: 10.1093/hmg/ddt540

Reijnders, M. R. F., Ansor, N. M., Kousi, M., Yue, W. W., Tan, P. L., Clarkson, K., et al. (2017). Assessment of de novo copy-number variations in Italian patients with compromised brain metabolism and oxidative stress. *J. Neurochem.* 146, 474–492. doi: 10.1111/jnc.14461

Sarkozy, A., Dligo, M. C., and Dallapiccola, B. (2008). Leopold syndrome. *Orphanet J. Rare Dis.* 3:13.

Sathanasivam, K., Neueder, A., Gipson, T. A., Landles, C., Benjamin, A. C., Bondulich, N., et al. (2004). Mutations in ARFGEF2 implicate vesicle trafficking in neural progenitor proliferation and migration in the human cerebral cortex. *Neuropathol. Appl. Neurobiol.* 30, 430–443.

Schwarz, T. L. (2013). Mitochondrial trafficking in neurons. *Cold Spring Harb. Perspect. Biol.* 5:13.

Schwartz, M. A., and Shattil, S. J. (2000). Signaling networks linking integrins and Raft-dependent mechanism and influences its cellular localization and carboxymethyl-phosphate synthetase (CPase) activity. *J. Biol. Chem.* 275, 1096–1105. doi: 10.1074/jbc.m114.532713

Sato, T., Akasu, H., Shimono, W., Matsu, C., Fujiwara, Y., Shibagaki, Y., et al. (2015). Rho protein binds CAD (carboxymethyl-phosphate synthetase 2, aspartate transcarbamoylase, and dihydroleotide) protein in a GTP- and effector domain-dependent manner and correlates with endoplasmic reticulum stress. *Neuropharmacol. Appl. Neurobiol.* 33, 523–532.

Schoneborn, H., Raudzus, F., Cupp, M., Neumann, S., and Heumann, R. (2018). Perspectives of RAS and RHEB GT-Pase signaling pathways in regenerating brain neurons. *Int. J. Mol. Sci.* 19:4052.

Schwartz, M. A., and Shattil, S. J. (2000). Signaling networks linking integrins and Rho family GTPases. *Trends Biochem. Sci.* 25, 388–391. doi: 10.1016/s0968-0004(00)01605-4

Schwarz, T. L. (2013). Mitochondrial trafficking in neurons. *Cold Spring Harb. Perspect. Biol.* 5:a011304.

Segev, N. (2001). Ypt/rab gt-pases: regulators of protein trafficking. *Sci. STKE* 2001re11. doi: 10.1126/stke.2001.100.re11

Shahani, N., Huang, W. C., Varnum, M., Page, D. T., and Subramaniam, S. (2017). Forebrain depletion of Rho GT-Pase elicits spatial memory deficits in mice. *Neurobiol. Aging* 50, 134–143. doi: 10.1016/j.neurobiolaging.2016.11.006

Shahani, N., Pryor, W., Swarnkar, S., Kholidilov, N., Thinakaran, G., Burke, R. E., et al. (2014). Rho GT-Pase regulates beta-secretase levels and amyloid beta generation. *J. Biol. Chem.* 289, 5799–5808. doi: 10.1074/jbc.m113.532713

Shao, H., and Andres, D. A. (2000). A novel RalGGEF-like protein, RGL3, as a candidate effector for Rit and Ras. *J. Biol. Chem.* 275, 26914–26924.

Sheen, V. L., Ganesh, V. S., Topcu, M., Sebire, G., Bodell, A., Hill, R. S., et al. (2004). RhoGEF2 implicate vesicle trafficking in neural progenitor proliferation and migration in the human cerebral cortex. *Nat. Genet.* 36, 69–76. doi: 10.1038/ng1276

Shen, W., Wu, B., Zhang, Z., Dou, Y., Rao, Z. R., Chen, Y. R., et al. (2006). Activity-induced rapid synaptic maturation mediated by presynaptic cdc42 signaling. *Neuron* 50, 401–414. doi: 10.1016/j.neuron.2006.03.017
Sheng, Z. H. (2014). Mitochondrial trafficking and anchoring in neurons: new insight and implications. J. Cell Biol. 204, 1087–1098. doi: 10.1083/jcb.201312123

Shenoy, S. K., and Lefkowitz, R. J. (2011). beta-Arrestin-mediated receptor trafficking and signal transduction. Trends Pharmacol. Sci. 32, 521–533. doi: 10.1016/j.tips.2013.05.002

Shi, G. X., and Andres, D. A. (2005). Rit contributes to nerve growth factor-induced neuronal differentiation via activation of B-Raf-extracellular signal-regulated kinase and p38 mitogen-activated protein kinase cascades. Mol. Cell. Biol. 25, 830–846. doi: 10.1128/mcb.25.2.830-846.2005

Shi, G. X., Cai, W., and Andres, D. A. (2011). The Ras-ERK-ETS-signaling pathway is a drug target for longevity. Cell 146, 72–83. doi: 10.1016/j.cell.2015.06.023

Sokolov, A. M., Seluzicki, C. M., Morton, M. C., and Feliciano, D. M. (2018). Dendrite growth and the effect of ectopic Rheb expression on cortical neurons. Neurosci. Lett. 671, 140–147. doi: 10.1016/j.neulet.2018.02.021

Stevenson, D. A., Viskochil, D. H., Rope, A. F., and Carey, J. C. (2006). Clinical and molecular anatomy of a trafficking organelle. Cell 127, 597–600.

Stornetta, R. L., and Zhu, J. J. (2011). Ras and Rap signaling in synaptic plasticity and mental disorders. Neuroscientist 17, 54–78. doi: 10.1177/1073858410356652

Subramaniam, S., Napolitano, F., Mealer, R. G., Kim, S., Errico, F., Barrow, R., et al. (2011). Rheas, a striatal-enriched small G protein, mediates mTOR signaling and L-DOPA-induced dyskinesia. Nat. Neurosci. 15, 191–193. doi: 10.1038/nn.2994

Subramaniam, S., Sixt, K. M., Barrow, R., and Snyder, S. H. (2009). Rheas, a striatal specific protein, mediates mutant-huntingtin cytotoxicity. Science 324, 1327–1330. doi: 10.1126/science.1172871

Sugita, H., Yasuda, S., Katsurabayashi, S., Kawano, H., Endo, K., Takasaki, K., et al. (2015). Rheb activation disrupts spine synapse formation through accumulation of syntenin in tuberous sclerosis complex. Nat. Commun. 6:6842.

Sun, W., Samimi, H., Gamez, M., Zare, H., and Frost, B. (2018). Pathogenic tau-induced preRNA depletion promotes neuronal death through transposable element dysregulation in neurodegenerative tauopathies. Nat. Neurosci. 21, 1038–1048. doi: 10.1038/s41593-018-0194-1

Swanson, A. M., Depoy, L. M., and Gourley, S. L. (2017). Inhibiting Rho kinase promotes goal-directed decision making and blocks habitual responding for cocaine. Nat. Commun. 8:1861.

Tada, H., Taira, Y., Morichika, K., and Kinoshita, T. (2016). Mitochondrial trafficking through RhoT1 is involved in the aggregation of germline granule components during primordial germ cell formation in Xenopus embryos. Dev. Growth Differ. 58, 641–650. doi: 10.1111/dgd.12310

Tajan, M., De Rocca Serra, A., Valet, P., Eduard, T., and Yart, A. (2015). SHP2 sail from physiology to pathology. Eur. J. Med. Genet. 58, 509–525. doi: 10.1016/j.ejmg.2015.08.005

Tajan, M., Paccoud, R., Branka, S., Eduard, T., and Yart, A. (2018). The RASopathy family: consequences of germline activation of the RAS/MAPK pathway. Endocr. Rev. 39, 676–700. doi: 10.1210/er-2017–00232

Takai, Y., Sasaki, T., and Matozaki, T. (2001). Small GTP-binding proteins. Physiol. Rev. 81, 153–208.

Takamori, S., Holt, M., Stenius, K., Lemke, E. A., Gronborg, M., Riedel, D. et al. (2006). Molecular anatomy of a trafficking organelle. Cell 127, 831–846.

Tansey, K. E., Rees, E., Linden, D. E., Ripke, S., Chambert, K. D., Moran, J. L., et al. (2016). Common alleles contribute to schizophrenia in CNVR carriers. Mol. Psychiatry 21:1153. doi: 10.1038/mp.2015.170

Tartaglia, M., Gelb, B. D., and Zenker, M. (2011). Noonan syndrome and clinically related disorders. Best Pract. Res. Clin. Endocrinol. Metab. 25, 161–179. doi: 10.1016/j.beem.2010.09.002

Teodoro, R. O., Pekkurnaz, G., Naser, A., Higashi-Kovtun, M. E., Balakireva, M., Mclachlan, I. G., et al. (2013). Rab mediates activity-dependent growth of postsynaptic membranes via recruitment of the exocyst. EMBO J. 32, 2039–2055. doi: 10.1002/emboj.2013.147

Tidman, W. E., and Rauen, K. A. (2016a). Expansion of the RASopathies. Curr. Genet. Med. Rep. 4, 57–64. doi: 10.4103/0214-016-0010-7

Tidman, W. E., and Rauen, K. A. (2016b). Pathogenetics of the RASopathies. Hum. Mol. Genet. 25, R123–R132.

Tsika, E., and Moore, D. J. (2013). Contribution of GTPase activity to LRRK2-associated Parkinson disease. Small GTPases 4, 164–170. doi: 10.4161/gtp.25130

Tyagi, R., Shahani, N., Gorgen, L., Ferretti, M., Pryor, W., Chen, P. Y., et al. (2015). RhoB inhibits protein synthesis by activating the PERK-eIF2alpha signaling cascade. Cell Rep. 10, 684–693.

Udayar, V., Buggia-Prevot, V., Guerreiro, R. L., Siegel, G., Rambabu, N., Soohoo, A. L., et al. (2013). A paired RNAi and RabGAP overexpression screen identifies Rab11 as a regulator of beta-amyloid production. Cell Rep. 5, 1536–1551. doi: 10.1016/j.celrep.2013.12.005

Ulrich, M., Weber, M., Post, A. M., Popp, S., Grein, J., Zechnier, M., et al. (2018). OCD-like behavior is caused by dysfunction of thalamo-amygdaloid circuits and upregulated TrkB/ERK-MAPK signaling as a result of SPRED2 deficiency. Mol. Psychiatry 23, 445–458. doi: 10.1038/mp.2016.232

Uno, T., Furutani, M., Watanabe, C., Sakamoto, K., Uno, Y., Kanamaru, K., et al. (2016). Rab proteins in the brain and corpus allatum of Bombyx mori. Histochem. Cell Biol. 146, 59–69. doi: 10.1007/s00418-016-1422-y

Urano, J., Ellis, C., Clark, G. J., and Tamanoi, F. (2001). Characterization of Rho functions using yeast and mammalian systems. Methods Enzymol. 333, 217–231. doi: 10.1016/S0076-6879(01)33014-3

Van Der Merwe, C., Jalali Sefid Dashti, Z., Christoffers, A. L., Boos, B., and Bardien, S. (2015). Evidence for a common biological pathway linking three Parkinson’s disease-causing genes: parkin, PINK1 and DJ-1. Eur. J. Neurosci. 41, 1113–1125. doi: 10.1111/ejn.12872

Van Trier, D. C., Rinne, T., Noordam, K., Draaisma, J. M., and Van Der Burgt, I. (2017). Phenotypic expression in a large Noonan syndrome family segregating a novel SOS1 mutation. Am. J. Med. Genet. A 173, 2968–2972. doi: 10.1002/ajmg.a.38466

Veltel, S., Gasper, R., Eisenacher, E., and Wittinghofer, A. (2008a). The retinitis pigmentosa G2 product is a GTPase-activating protein for Arf-like 3. Nat. Struct. Mol. Biol. 15, 373–380. doi: 10.1038/nsm.1396

Veltel, S., Kravchenko, A., Ismail, S., and Wittinghofer, A. (2008b). Specificity of Arl2/Arl3 signaling is mediated by a ternary Arl3-effector-GAP complex. FEBS Lett. 582, 2501–2507. doi: 10.1016/j.febslet.2008.05.053
Wakioka, T., Sasaki, A., Kato, R., Shouda, T., Matsumoto, A., Miyoshi, K., et al. (2001). Spped is a Sprouty-related suppressor of Ras signalling. Nature 412, 647–651. doi: 10.1038/35088082

Wang, H. and Jiang, C. (2013). RAB38 confers a poor prognosis, associated with malignant progression and subtype preference in glioma. Oncol. Rep. 30, 2350–2356. doi: 10.3892/or.2013.2730

Wang, L., Popko, B., and Roos, R. P. (2011). The unfolded protein response in familial amyotrophic lateral sclerosis. Hum. Mol. Genet. 20, 1008–1015. doi: 10.1093/hmg/ddq546

Wang, W., Ju, Y. X., Zhou, Q. X., Tang, J. X., Li, M., Zhang, L., et al. (2017). The small GTPase Rac1 contributes to extinction of aversive memories of drug withdrawal by facilitating GABAA receptor endocytosis in the vmPFC. J. Neurosci. 37, 7906–7910. doi: 10.1523/jneurosci.3859-16.2017

Ward, M. E., Taubes, A., Chen, R., Miller, B. L., Sephton, C. F., Gelfand, J. M., et al. (2016). Early retinal neurodegeneration and impaired Ran-mediated nuclear import of TDP-43 in progranulin-deficient FTLD. J. Exp. Med. 211, 1937–1945. doi: 10.1084/jem.20140214

Watabe-Uchida, M., Govek, E. E., and Van Aelst, L. (2006). Regulators of Rho GT Pases in neuronal development. J. Neurosci. 26, 10633–10635. doi: 10.1523/jneurosci.4804-06.2006

Weis, K. (2003). Regulating access to the genome: nucleocytoplasmic transport throughout the cell cycle. Cell 112, 441–451. doi: 10.1016/s0092-8674(03)00882-5

Wennerberg, K., Rossman, K. L., and Der, C. J. (2005). The Ras superfamily at a glance. J. Cell Sci. 118, 843–846. doi: 10.1242/jcs.01660

Williams, V. C., Lucas, J., Babcock, M. A., Gutmann, D. H., Korf, B., and Maria, B. L. (2009). Neurofibromatosis type I revisited. Pediatrics 123, 124–133.

Wilson, G. R., Sim, J. C., Mclean, C., Giannandrea, M., Galea, C. A., Risley, J. R., et al. (2014). Mutations in RAB39B cause X-linked intellectual disability and early-onset Parkinson disease with alpha-synuclein pathology. Am. J. Hum. Genet. 95, 729–735. doi: 10.1016/j.ajhg.2014.10.015

Xiao, F., He, M., Wang, X. F., Xi, Z. Q., Li, J. M., Wu, Y., et al. (2007). [Overexpression of the Cdc42 in the brain tissue of human with intractable temporal epilepsy]. Zhonghua Yi Xue Za Zhi 87, 2030–2032.

Xu, W., Tan, L., and Yu, J. T. (2015). The role of PICALM in Alzheimer’s disease. Mol. Neurobiol. 52, 399–413. doi: 10.1007/s12031-014-8878-3

Yan, T., Wang, L., Gao, J., Siedlak, S. L., Huntley, M. L., TerBushas, P., et al. (2018). Rab10 phosphorylation is a prominent pathological feature in presenilin 1 knock-in mice. J. Mol. Neurosci. 64, 209–222. doi: 10.1007/s12031-015-0544-3

Zafar, S., Younas, N., Correia, S., Shafiq, M., Tahir, W., Schmitz, M., et al. (2017). Strain-specific altered regulatory response of Rab7a and tau in creutzfeldt-jakob disease and Alzheimer’s disease. Mol. Neurobiol. 54, 697–709. doi: 10.1007/s12031-016-9694-8

Zago, G., Biondini, M., Camonis, J., and Parrini, M. C. (2017). A family affair: a Ran-exocytosed network links Ras, Rac, Rho signaling to control cell migration. Small GTPases doi: 10.1080/21541248.2017[Epub ahead of print].

Zamboni, V., Jones, R., Umbach, A., Ammoni, A., Passafaro, M., Hirsch, E., et al. (2018). Rho GTPases in intellectual disability: from genetics to therapeutic opportunities. Int. J. Mol. Sci. 19, 1821.

Zhai, J., Zhang, L., Mozolsivc-Petrovic, J., Jian, X., Thomas, J., Homma, K., et al. (2015). Inhibition of cytohesins protects against genetic models of motor neuron disease. J. Neurosci. 35, 9088–9105. doi: 10.1523/jneurosci.5032-13.2015

Zhang, H., Hanke-Gogokhia, C., Jiang, L., Li, X., Wang, P., Gerstner, C. D., et al. (2015). Mistrafficking of prenylated proteins causes retinitis pigmentosa 2. FASEB J. 29, 932–942. doi: 10.1096/fj.14-57915

Zhang, Y., Liu, J., Luan, G., and Wang, X. (2015). Inhibition of the small GTPase Cdc42 in regulation of epileptic-seizure in rats. Neuroscience 289, 381–391. doi: 10.1016/j.neuroscience.2014.12.059

Zhang, H., Petit, G. H., Gaughwin, P. M., Hansen, C., Ranganathan, S., Zuo, X., et al. (2013). NRF2 rescues hippocampal cholinergic neuronal markers, restores neurogenesis, and improves the spatial working memory in a mouse model of Huntington’s disease. J. Huntington Dis. 2, 69–82.

Zhang, L., Zhang, W., Gao, Z., Zhang, H., Zhang, Y., Yu, Y., et al. (2018). Ras and Rap signal bidirectional synaptic plasticity via distinct subcellular microdomains. Neurosci. 98, 738–800.e4. doi: 10.1016/j.neuro.2018.03.049

Zhang, X., Huang, T. Y., Yancey, J., Luo, H., and Zhang, Y. W. (2018). Role of Rab GT Pases in Alzheimer’s disease. ACS Chem. Neurosci. 10, 828–838.

Zhao, Z., Sagare, A. P., Ma, Q., Halliday, M. R., Kong, P., Kisler, K., et al. (2015). Central role for PICALM in amyloid-beta blood-brain barrier transcytosis and clearance. Nat. Neurosci. 18, 978–987. doi: 10.1038/nn.4025

Zheng, X., Liang, Y., He, Q., Yao, R., Bao, W., Bao, L., et al. (2014). Current models of mammalian target of rapamycin complex 1 (mTORC1) activation by growth factors and amino acids. Int. J. Mol. Sci. 15, 20753–20769. doi: 10.3390/ijms151120753

Zhuo, C., Hou, W., Lin, C., Hu, L., and Li, J. (2017). Potential value of genomic copy number variations in schizophrenia. Front. Mol. Neurosci. 10:204. doi: 10.3389/fnmol.2017.00204

Zimmering, M. B. (2018). Circulating Neurotoxic 5-HT2A receptor agonist autoantibodies in adult type 2 diabetes with Parkinson’s disease. J. Endocrinol. Diab. 5, 1–11. doi: 10.15226/2374-6890/5/2/00102

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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