nArgBP2-SAPAP-SHANK, the core postsynaptic triad associated with psychiatric disorders

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Abstract
Despite the complex genetic architecture, a broad spectrum of psychiatric disorders can still be caused by mutation(s) in the same gene. These disorders are interrelated with overlapping causative mechanisms including variations in the interaction among the risk-associated proteins that may give rise to the specific spectrum of each disorder. Additionally, multiple lines of evidence implicate an imbalance between excitatory and inhibitory neuronal activity (E/I imbalance) as the shared key etiology. Thus, understanding the molecular mechanisms underlying E/I imbalance provides essential insight into the etiology of these disorders. One important class of candidate risk genes is the postsynaptic scaffolding proteins, such as nArgBP2, SAPAP, and SHANK that regulate the actin cytoskeleton in dendritic spines of excitatory synapses. This review will cover and discuss recent studies that examined how these proteins, especially nArgBP2, are associated with psychiatric disorders. Next, we propose a possibility that variations in the interaction among these proteins in a specific brain region might contribute to the onset of diverse phenotypes of psychiatric disorders.

Introduction
In neural circuits, the balance between excitatory and inhibitory neuronal activity (E/I balance) refers to the relative degree of excitatory and inhibitory neuronal activity1. The amount of excitatory vs. inhibitory inputs modulates the excitability and function of a single neuron, and the integration of E/I drive in a group of neurons determines the strength of neuronal activity in a certain brain circuit of a particular brain region2,3. Thus, the ratio between excitation and inhibition has been recognized as a crucial measure for assessing brain fitness as its imbalance is implicated in many psychiatric disorders, including autism spectrum disorder (ASD)4, bipolar disorder (BD)5, and schizophrenia (SCZ)5,6. However, measuring the E/I ratio is complicated because mixtures of disparate excitatory and inhibitory signals may represent various circuits in different brain regions. Even within a single circuit, a large flexibility between excitation and inhibition affects varying aspects of neuronal function. Despite these challenges, mutations in many of the postsynaptic proteins that affect the formation or maintenance of either excitatory or inhibitory synapses have been identified as a causative factor for the dysregulation of the E/I balance in psychiatric disorders7. Indeed, recent studies indicate that assembly of the scaffolding proteins at excitatory synapses that regulate the actin cytoskeleton in dendritic spines is critical for maintaining the synaptic E/I balance and that either up- or downregulation of these molecules is implicated in various psychiatric disorders (Table 1).

In this review, we summarize recent studies that investigated how perturbations in the scaffolding proteins at excitatory synapses, especially focusing on nArgBP2, lead to an E/I imbalance. In addition, we propose a hypothesis that a shift in the balance of synaptic actin dynamics caused by altered interactions among nArgBP2-SAPAP-SHANK, core-postsynaptic proteins, is an important factor in the manifestation of an E/I imbalance in a specific brain region that accounts for various psychiatric disorders.
### Table 1 Table showing the SAPAP, SHANK, and nArgBP2 subtypes expressed in the brain and the corresponding CNS diseases

| Subtype   | CNS disease                        | Expression level | References |
|-----------|------------------------------------|------------------|------------|
| SAPAP1    | Schizophrenia                      | ↑                | 28         |
|           | Alzheimer’s disease                | ↓                | 88         |
|           | Major depressive disorder          | ↓                | 29         |
| SAPAP2    | Schizophrenia                      | ↑                | 32         |
|           | Fragile X mental retardation       | ↑                | 89         |
|           | Post-traumatic stress disorder     | ↓                | 30         |
|           | Autism spectrum disorder           | ↓                | 31         |
| SAPAP3    | Trichotillomania                   | ↓                | 35–37      |
|           | Obsessive compulsive disorder      | ↓                | 33, 35–37  |
|           | Parkinson’s disease                | ↓                | 90         |
|           | Schizophrenia                      | ↓                | 84, 91     |
| SAPAP4    | Cerebellar ataxia                  | ↓                | 92         |
|           | Bipolar disorder                   | ↓                | 93         |
| SHANK1    | Autism spectrum disorder           | ↓                | 50, 51     |
|           | Schizophrenia                      | ↓                | 52, 53     |
|           | Alzheimer’s disease                | ↓                | 94, 95     |
| SHANK2    | Autism spectrum disorder           | ↓                | 31, 55, 96 |
|           | Schizophrenia                      | ↓                | 57, 97     |
|           | Bipolar disorder                   | ↓                | 97, 98     |
|           | Intellectual disability            | ↓                | 33, 54–56, 96 |
|           | Alzheimer’s disease                | ↑                | 99         |
| SHANK3    | Autism spectrum disorder           | ↓                | 86, 100–104|
|           | Epilepsy                           | ↓                | 105, 106   |
|           | Obsessive compulsive disorder      | ↓                | 107, 108   |
|           | Attention-deficit/ hyperactivity disorder | ↑    | 104, 109   |
|           | Phelan–McDermid syndrome            | ↓                | 46, 47, 110–112 |
|           | Schizophrenia                      | ↓                | 58, 60, 87, 108, 113–115 |
|           | Bipolar disorder                   | ↑                | 59, 111, 116, 117 |
|           | Alzheimer’s disease                | ↓                | 94, 95     |
| nArgBP2   | Bipolar disorder                   | ↓                | 73, 74, 118 |
|           | Intellectual disability            | ↓                | 65         |

The upward or downward arrow signifies up- or downregulation/mutation, respectively.

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**Dendritic spine regulation as a common mechanism of psychiatric disorders**

Most studies on excitatory synaptic transmission linked to E/I imbalance are focused on the proteins that regulate dendritic spines. Dendritic spines are tiny protrusions on the dendrites and serve as a structural unit, where excitatory synaptic transmission occurs\(^5\). Spines integrate excitatory signals into the output passed on to another neuron in the brain circuit\(^8\). Spines are classified according to their morphological features such as shape and size since their morphology is highly correlated with their functional properties. Spines actively participate in the formation of synapses and neuronal circuits during development\(^10\), whereas activity-dependent spine maintenance or elimination is important for the remodeling of established neuronal circuits during postnatal and adolescent periods\(^11,12\). Persistent changes in synaptic strength during synaptic plasticity also involve structural changes of spines. Indeed, spines are morphologically regulated to meet the dynamic demands of the brain and are intimately linked to higher brain function\(^13\)\(^–\)\(^16\). Molecular pathways involving the regulation of spines include cytoskeletal remodeling, trans-synaptic adhesion, receptor trafficking, protein translation, ubiquitination, and gene expression\(^13,14\).

The cytoplasm of dendritic spines is enriched with highly branched filamentous actin (F-actin) located exactly beneath the postsynaptic density (PSD). The actin cytoskeleton stabilizes and modulates the dynamic dendritic spine structure in response to neuronal activity\(^15,16\), and the regulation of such dynamics is critical for the morphological changes, maturation, and physiological function of spines\(^17\). A recent study using super-resolution imaging showed that the actin cytoskeleton is unevenly distributed and rapidly reorganized within synapses\(^18\).

The dendritic spine contains a large number of scaffolding proteins, including SHANK (or Pro-SAP), SAPAP (or GKAP), and nArgBP2, which share highly conserved domains for protein–protein interactions. These proteins can interact with multiple proteins simultaneously to physically connect PSD components and organize binding partners into a functional unit to enhance postsynaptic signaling\(^19\) (Fig. 1). The specialized functional network composed of these proteins provides a direct link between membrane receptors, cell adhesion molecules, and the actin cytoskeleton, thus facilitating activity-dependent dendritic remodeling, which is critical for synaptogenesis and synaptic plasticity\(^15,16\). Anatomical analysis often reveals altered dendritic spine morphology in the brains of patients with SCZ, intellectual disabilities, and ASDs\(^20\). Indeed, most genetic human risk factors for these disorders are associated with the signaling of actin cytoskeleton dynamics in dendritic spines.
spines. Accordingly, various studies have reported that numerous psychiatric disorders are characterized by dendritic abnormalities, including aberrant spine density and morphology, which are most likely to significantly affect excitatory drive and subsequently E/I balance in the brain circuit.

Core postsynaptic proteins associated with psychiatric disorders

SAPAP

The four members of the guanylate kinase-associated protein (GKAP) family were originally identified as proteins that interact with the GK domain of PSD95 and named SAP90/PSD95-associated protein (SAPAP) 1–4. SAPAPs consist of a 14-amino acid repeat domain, a dynein light chain (DLC) domain, and a GKAP homology (GH1) domain. As a scaffold protein, SAPAP binds to PSD95, synaptic scaffolding molecule (S-SCAM), nArgBP2 and dynein light chain via its N-terminal domain, while it interacts with the PDZ domain of ProSAPs/SHANKs through its C-terminal domain (Fig. 1).

Implications of SAPAPs in psychiatric disorders

A previous study found that SAPAP1 immunoreactivity is significantly increased in the nucleus accumbens of unmedicated patients with SCZ. SAPAP1 is also implicated in recurrent major depressive disorder according to a report from a study of Mexican American individuals. Screening of genomic DNA methylation patterns in a rat post-traumatic stress disorder (PTSD) model revealed that an increase in a specific methylation site causes a reduction in SAPAP2 gene expression, thus pinpointing SAPAP2 as a possible target for PTSD. Some common and rare genetic variants of SAPAP2 have also been found to be associated with ASD, and increased SAPAP2 gene expression contributes to the pathogenesis of SCZ. Genetic deletion of SAPAP3 in mice causes behavioral abnormalities including increased anxiety and compulsive self-grooming, which are similar to symptoms exhibited by human patients with obsessive compulsive disorder (OCD) and phenotypes exhibited by other genetic animal models of OCD-like behaviors. OCD-like behaviors in SAPAP3-null mice have been indicated in several recent human genetics studies of the role of SAPAP3 in obsessive compulsive spectrum disorder (OCSD). SHANK

The SH3 and multiple ankyrin repeat domains (SHANK) family is a group of scaffold proteins that contain ankyrin repeat domains, a SH3 domain, one PDZ domain, a proline-rich region (PRD), and a sterile alpha motif (SAM) domain. The ankyrin repeat domain, containing six ankyrin repeats, interacts with the PSD protein SHARPIN and binds to the cytoskeleton through an interaction with α-spectrin (also known as α-fodrin). The PDZ domain of SHANK interacts with SAPAP1 and the GluR1 subunit of AMPA receptors and, therefore, is important for dendritic spine formation and synaptic transmission. The PRD binds to Homer and cortactin, and such an interaction is important for cytoskeleton regulation as well as synaptic transmission and plasticity. The C-terminal SAM domain is important for self-multimerization of the protein and is required for the localization of SHANK to the PSD (Fig. 1). SHANK binds to SAPAP, which in turn binds to PSD95 to form a PSD95/SAPAP/SHANK postsynaptic complex.
Implications of SHANKs in psychiatric disorders

SHANK genes were first identified in studies of Phelan–McDermid syndrome (PMS), a neurodevelopmental disorder that is caused by chromosome 22q13.3 deletion and characterized by autistic-like behaviors, hypotonia, and delayed or absent speech. Moreover, mutations or disruptions in the SHANK gene family account for ~1% of all patients with ASD. SHANK1 (also known as ProSAP3) deletions and mutations have been reported to cause broad autism phenotypes in males. A recent study also found a de novo SHANK1 mutation in a female with ASD. Lennerts et al. found that the T allele of SNP rs3810280 in the SHANK1 promoter is associated with reduced auditory working memory in patients with SCZ and Fromer et al. reported a de novo SHANK1 frameshift mutation in a female schizophrenia patient.

Several studies have identified deleterious mutations of SHANK2 (also known as ProSAP1) in patients with ASD and mild/moderate intellectual disability (ID) . Missense variants of SHANK2 identified in SCZ patients correspond to a mutation in hippocampal neurons that leads to a loss of presynaptic contacts and reduced clustering of SHANK2 at synapses.

SHANK3 (also known as ProSAP2) is the best studied among the three SHANK family members, and its mutant mice exhibit autistic-like behaviors, including impaired social interaction and repetitive behaviors. SHANK3 was first recognized in PMS and later in ASD with symptoms that include ID, autistic behaviors, hypotonia, and significant language impairment. In addition, duplication of the SHANK3 gene is often found in patients diagnosed with BD, and mice with an extra copy of SHANK3 exhibit manic-like phenotypes. A recent study further found that mice with the ASD-linked InsG3680 mutation in SHANK3 show defective synaptic transmission in the striatum and impaired juvenile social interaction, coinciding with the early onset of ASD symptoms, while adult mice carrying the schizophrenia-linked R1117X mutation show profound synaptic defects in the prefrontal cortex and social dominance behavior.

nArgBP2

Domain structure of nArgBP2

nArgBP2 is a neural variant of ArgBP2 (Arg binding protein 2, also known as SORBS2) and was first cloned from the rat brain as an SAPAP-binding protein. The full-length protein is composed of 1196 amino acids containing multiple domains for protein–protein interaction including a sorbin homology (SoHo) domain in the N-terminal region and three Src homology 3 (SH3) domains in the C-terminal region. nArgBP2 has one zinc-finger motif in the middle region (Fig. 1).

Expression patterns of nArgBP2 mRNAs and proteins

The SORBS2 gene encodes multiple transcripts including four ArgBP2 isoforms (α, β, γ, and δ isoform) and nArgBP2 through alternative RNA splicing. ArgBP2/nArgBP2 isoforms are widely expressed in human tissues and are especially abundant in the brain, heart, pancreas, and colon. A transcript corresponding to an nArgBP2-specific exon is detected only in the brain tissue and exclusively in neurons. In the brain, nArgBP2 mRNA is highly expressed in the isocortex, hippocampus, cortical subplate, striatum, thalamus, and hypothalamus, the majority of which are regions of the brain associated with BD. At the protein level, nArgBP2 is only detected in the brain with a high expression level in the cortex, amygdala, and dentate gyrus and moderate expression level in the striatum, lateral habenula, and thalamus. Within cortical regions, immunoreactivity for nArgBP2 is more intense in layers I–III in the neocortex and layer I of the piriform cortex. In the DG, nArgBP2 is specifically enriched at the edge of the molecular layer.

Protein interactions of nArgBP2

nArgBP2 is a scaffold protein that controls the balance between adhesion and motility by modulating the function of multiple signaling pathways that converge on the actin cytoskeleton. The N-terminal SoHo domain interacts with α2-spectrin, and the three SH3 domains have partially overlapping binding partners, with the second SH3 having the most interactors including SAPAP, synaptopodin, synaptojanin1/2, vinculin, Abl, Cbl, and dynamin1/2. Other interactors include the actin-regulating Wiskott–Aldrich syndrome protein family verprolin homologous protein (WAVE) 1 and 2 and components of a WAVE regulatory complex (PIR121 and Nap1). ArgBP2 mediates the formation of a complex containing Abl and Cbl, which promotes the Abl-dependent phosphorylation of Cbl and the ubiquitination by Cbl of both Abl and ArgBP2. In the brain, Abl interacts with Abelson interacting protein-1 (Abi-1), which binds to SHANK and is essential for dendrite morphogenesis and synapse formation. nArgBP2 interacts with SHANK either directly or indirectly through SAPAP, suggesting a possible network formation among nArgBP2, SAPAP, and SHANK.

Synaptic localization of nArgBP2

In rat brain subcellular fractions, nArgBP2 is detected in the cytosol of the synaptosome but is also enriched in the PSD fraction. Immunocytochemistry analysis with specific nArgBP2 antibodies indicates that nArgBP2...
colocalizes with F-actin and is enriched in both dendritic and axonal terminals in early developing neurons. In mature neurons, nArgBP2 is mainly enriched in dendrites, especially in dendritic spines in which it colocalizes with the excitatory postsynaptic scaffolding protein PSD95. Dendritic clusters of nArgBP2 are also juxtaposed with vesicular glutamate transporter 1 (vGLUT1) puncta in spiny neurons. In contrast, nArgBP2 rarely overlaps with the inhibitory postsynaptic scaffolding protein gephyrin in spiny neurons. Collectively, these observations show that nArgBP2 primarily localizes to excitatory synapses in spiny pyramidal neurons and plays a specific functional role in these excitatory synapses.

nArgBP2 in dendritic spine formation

Recently, Zhang et al. found that dendritic arborization of DG granule cells in nArgBP2 KO mice shows much less complexity with a significantly reduced number of dendritic branch points than those in wild-type (WT) littermates. We also found that the density of total dendritic protrusions and the proportion of mushroom-shaped spines are dramatically decreased with nArgBP2 knockdown (KD). Additionally, the expression level of the active form of WAVE1 is increased in nArgBP2 KD, and Rac1 activity is enhanced, leading to p21-activated kinase (PAK) activation and cofilin inactivation. Dendritic spines in KD neurons are highly motile, and the pool of dynamic actin downstream of Rac1 activation is significantly increased accordingly.

nArgBP2 in the regulation of excitatory synaptic formation and transmission

nArgBP2 KD causes a specific and dramatic reduction in the number of spine-synapses, which is consistent with the decreased number of mushroom-shaped spines in KD neurons (Fig. 2). Furthermore, the mean frequency of miniature excitatory postsynaptic currents (mEPSCs) is significantly decreased compared to that in control neurons, while that of miniature inhibitory postsynaptic currents (mIPSCs) is not affected. Consistently, in nArgBP2 KO mice, the mean frequency of mEPSCs is also significantly reduced compared to that in WT littermates. These findings indicate that nArgBP2 functions to regulate spine morphogenesis and subsequent spine-synapse formation at glutamatergic synapses and that its...
ablation causes a robust and selective inhibition of excitatory synapse formation by controlling actin cytoskeleton dynamics (Fig. 2).

**Behavioral phenotypes of nArgBP2 KO mice and implications of nArgBP2 in psychiatric disorders**

*nArgBP2* KO mice have been reported to display manic/bipolar-like behavior including increased activity, compulsive/repetitive behavior, risk-taking behavior, hedonistic behavior, and anti-depressant-like behavior, resembling many aspects of symptoms in BD patients97. Additional behavioral phenotypes include altered long-term but not short-term object recognition memory, as well as impaired contextual fear memory98. A specific defect in contextual fear memory but not in conditioned fear memory implies that *nArgBP2* may have a more important role in the hippocampus than in the amygdala99, *nArgBP2* KO mice also show a reduced dendritic complexity of DG granule cells65, supporting the link between the mutation of *nArgBP2* and ID53. *nArgBP2* de novo mutations are also found in SCZ patients53.

**Postsynaptic triad of nArgBP2-SAPAP-SHANK, a convergent pathway of psychiatric disorders**

Data from a large-scale study revealed that there are a substantial number of individuals who simultaneously meet the criteria for two or more psychiatric disorders. For example, comorbid BD and OCD are relatively common among patients with a primary diagnosis of BD74. Studies have also found that as many as 27% of those with ASD also have symptoms of BD79,80. Similarly, there is a strong positive correlation between measures of the severity of both depression and anxiety symptoms81. Indeed, recent genome-wide genetic studies have further identified overlapping risk genes across the major psychiatric disorders, including SCZ, BD, major depressive disorder, and ASD80,82–84. These results indicate that dysregulation of the same gene can cause different types of disorders, further suggesting the existence of a convergent mechanism for various psychiatric disorders with multiple etiologies.

Recent studies suggest that deletion or overexpression of postsynaptic proteins, such as *nArgBP2*, SAPAP, and SHANK, leads to behavioral phenotypes that are similar to symptoms observed in human ASD, BD, SCZ, and OCD59,60,74,85. Deletion of SAPAP causes OCD-like behaviors33, some genetic variants of SAPAP2 are associated with ASD31, and increased SAPAP2 expression contributes to the pathogenesis of SCZ32. In addition, SHANK3 deletion or mutation is associated with ASD86, and its duplication or other mutations result in BD-like manic behaviors59 or SCZ-like behaviors87. Deletion of *nArgBP2* causes ID and BD-like symptoms65,74. Interestingly, SHANK binds to the GH1 domain of SAPAP directly via its PDZ domain. SAPAP binds to the SH3 domain of *nArgBP2* via its proline-rich region. *nArgBP2* and SHANK share a number of proteins as common binding partners (Fig. 1). Therefore, these three major postsynaptic proteins indeed interact with each other in dendritic spines of excitatory synapses such that the high incidence of comorbidity among psychiatric disorders is comprehensible. Although the underlying molecular mechanisms that connect the aberrant expression of these genes and behavioral consequences are still far from elucidated, E/I imbalance caused by dysregulation of the actin cytoskeleton in dendritic spines has been suggested as a shared key molecular mechanism.

Here, we propose a hypothesis that *nArgBP2*, SAPAP, and SHANK form a core scaffolding triad and together regulate actin cytoskeleton in dendritic spines. Different levels of expression or activity of this core triad may result in different phenotypes of psychiatric disorders in a brain region-specific manner, thus asserting that actin regulation by the core triad in dendritic spines is a convergent mechanism for psychiatric disorders (Fig. 3). Similar to each point of an equilateral triangle, these three proteins interact with each other to form a structural and functional postsynaptic scaffold that organizes multiple protein interactions to regulate the actin cytoskeleton in dendritic spines. Altered expression or mutation of either one or more of the proteins in the core triad in a specific brain region would break the balance of the interactome and induce defects in actin regulation, leading to spine structure abnormalities and, subsequently, to defects in the excitatory synaptic integrity. Depending on which individual protein is affected and, accordingly, which distinct protein network is disrupted, the E/I balance may be differently altered at molecular, synaptic, and circuit levels in a brain region-specific manner, and these differences will be the contributing factors for the diverse phenotypes of psychiatric disorders. Through the combination of genetic approaches and recently developed imaging techniques, the identification of critical brain regions and neuronal types in which the core triad protein complex of *nArgBP2*, SAPAP, and SHANK differentially regulates synaptic function will help us to test and advance this tempting hypothesis.

**Conclusion**

Considering the high diversity and complexity of psychiatric disorders, it is surprising that many risk genes are shared by multiple psychiatric disorders and that many of these risk genes are regulators of actin cytoskeleton signaling in dendritic spines. Consistently, accumulating evidence suggests that alterations in dendritic spine morphology are a shared molecular etiology across different psychiatric disorders. New strategies focusing on the convergent mechanism of psychiatric disorders involving the postsynaptic triad of *nArgBP2*, SAPAP, and SHANK may represent a potential therapeutic approach to the treatment of psychiatric disorders.
psychiatric disorders. We propose that nArgBP2, SAPAP, and SHANK form the core scaffolding triad to precisely mediate actin regulation in dendritic spines and that this serves as a convergent mechanism for different psychiatric disorders. Further studies on the brain region-specific regulation of actin dynamics by the core triad will be necessary to better understand the molecular mechanisms of various psychiatric disorders.

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Fig. 3 Hypothetical model proposing the postsynaptic triad of nArgBP2-SAPAP-SHANK as a convergent pathway of psychiatric disorders. nArgBP2, SAPAP, and SHANK interact with each other, forming a structural and functional postsynaptic scaffold. They also organize multiple interactomes to regulate the actin cytoskeleton. Alterations in the expression of either one or more of the proteins participating in the core triad would break the interactome balance and induce actin cytoskeleton dysregulation, leading to abnormal spine formation and morphogenesis, which consequently undermines excitatory synapse formation. Depending on levels of expression or activity of this core triad in a specific brain region, diverse levels of E/I imbalance may lead to the numerous phenotypes of psychiatric disorders. Thus, actin regulation by the core triad in dendritic spines is a convergent mechanism for various psychiatric disorders such as ASD, BD, OCD, and SCZ.

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