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The Role of Cell Adhesion Molecule IgSF9b at the Inhibitory Synapse and Psychiatric Disease

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Abstract

Understanding perturbations in synaptic function between health and disease states is crucial to the treatment of neuropsychiatric illness. While genome-wide association studies have identified several genetic loci implicated in synaptic dysfunction in disorders such as autism and schizophrenia, many have not been rigorously characterized. Here, we highlight immunoglobulin superfamily member 9b (IgSF9b), a cell adhesion molecule thought to localize exclusively to inhibitory synapses in the brain. While both pre-clinical and clinical studies suggest its association with psychiatric diseases, our understanding of IgSF9b in synaptic maintenance, neural circuits, and behavioral phenotypes remains rudimentary. Moreover, these functions wield undiscovered influences on neurodevelopment. This review evaluates current literature and publicly available gene expression databases to explore the implications of IgSF9b dysfunction in rodents and humans. Through a focused analysis of one high-risk gene locus, we identify areas requiring further investigation and unearth clues related to broader mechanisms contributing to the synaptic etiology of psychiatric disorders.

Keywords

Cell adhesion; Inhibitory synapse; Circuit development; Schizophrenia; Psychiatric disorders

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Author Contributions

JC conceived the manuscript outline, JC, CA, NR, and WJG wrote the paper.

Conflict of Interest

The authors declare no competing financial interests.

1. Cell Adhesion Molecules, Inhibitory Synapse Function, and the Curious Case of IgSF9b

Throughout the nervous system, cell adhesion molecules (CAMs) serve as both structural and functional links between neurons. These proteins are expressed on neuronal cell membranes and mediate interactions with the extracellular environment to support a variety of functions, including neurite outgrowth, cell differentiation, and the formation and development of synapses (Kozlova et al., 2020; Südhof, 2021). The diversity of CAMs is vast, and the expression of a particular CAM is often specific to cellular identity (Paul et al., 2017). This specificity of CAM expression in discrete cell types is highly relevant to synaptic function, as synaptic CAM diversity is hypothesized to underlie the complex wiring codes among synaptic partners (Favuzzi et al., 2019; Kim et al., 2021). In this framework, synaptic CAMs support the formation and function of various synapse types, each with a distinct complement of ionotropic and metabotropic receptors, intracellular second messengers, and ion channels (Paul et al., 2017). From an evolutionary perspective, the vast expansion of the synaptic proteome, of which CAMs are a vital component, is theorized to support the enhanced signaling capacity and functional specializations necessary for complex behavior in mammals (Emes et al., 2008). Thus, natural selection processes have given rise to CAMs that function in a particular synaptic niche.

While a panoply of proteins crucial to the function of excitatory synapses has been identified and characterized, the set of factors present at inhibitory synapses is only recently coming to light (Krueger-Burg et al., 2017). Immunoglobulin superfamily (IgSF) member 9b (IgSF9b) is a CAM found exclusively at inhibitory synapses and belongs to a large group of IgSF proteins that are expressed across synapse types in the developing and mature CNS (Leshchyns'ka and Sytnyk, 2016; Lu et al., 2017; Maness and Schachner, 2007). These cell surface glycoproteins are characterized by an extracellular immunoglobulin (Ig) domain, containing one to several Ig repeats. The extracellular Ig domains are protein interaction motifs, allowing IgSFs to participate in diverse homophilic and heterophilic protein-protein interactions (Lu et al., 2017). In the developing CNS, IgSFs play critical roles in axon outgrowth, neuronal migration, neuronal survival, and neuronal circuit development (Dityatev et al., 2008; Leshchyns'ka and Sytnyk, 2016; Maness and Schachner, 2007). In the mature CNS, IgSFs assist in neuroplasticity and neurotransmission via binding to extracellular ligands to initiate intracellular signaling cascades (Dityatev et al., 2008; Leshchyns'ka and Sytnyk, 2016). Expectedly, IgSFs have clinically relevant functions in excitatory and inhibitory synapses. Polymorphisms in genes encoding for IgSF proteins primarily expressed in the CNS are correlated with neuropsychiatric diseases such as autism spectrum disorders (ASD), major depressive disorder (MDD), bipolar disorder, and schizophrenia (SZ) (Lu et al., 2017; Shyn et al., 2011). Investigating these CAMs deepens our understanding of synaptic function, which is of immediate relevance to our overall knowledge of the neural circuits that govern behavior.

IgSF9b has been associated with both SZ and MDD by genome-wide association studies (GWAS) (Schizophrenia Working Group of the Psychiatric Genomics, 2014; Shyn et al., 2011). In addition to its implication in these disorders, preclinical models show that IgSF9b

plays a role in synaptic function and affective behavioral processes. In terms of tissue expression patterns in rats and humans, IgSF9b was found to be mostly expressed in the brain, predominantly in the cortex and cerebellum (proteinatlas.org) (Sjostedt et al., 2020; Woo et al., 2013). In the rat brain, IgSF9b expression peaks at around three postnatal weeks (Woo et al., 2013), suggesting that this gene is developmentally regulated at a delayed time point after initial cortical synapse formation (Favuzzi et al., 2019). Importantly, IgSF9b was found localized to inhibitory but not excitatory synapses, and in particular, may be important specifically for gamma amino-butyric acid (GABA)ergic contacts onto inhibitory neurons (Woo et al., 2013). In the clinical realm, one single-nucleotide polymorphism in the IgSF9b gene locus has been specifically associated with negative symptoms of SZ (Fabbri and Serretti, 2017), a chronically debilitating and often treatment-resistant domain of the disorder. This review will focus on IgSF9b to shed light on current findings and discuss promising avenues for future research, as many details related to the function of IgSF9b remain elusive. Additionally, we explore open-access RNA-Seq data to better assess IgSF9b expression dynamics throughout human brain development and within transcriptionally distinct cell types in the mouse isocortex and hippocampus. Through a comprehensive discussion of one psychiatric risk gene, we highlight that GABAergic synaptic organizers hold distinct influences on neural circuit development and function, which are relevant to the pathophysiology of psychiatric disorders.

2. What are the known functions of IgSF9b in the mammalian nervous system?

2.1. In Vitro Findings

IgSF9 protein members are an evolutionarily conserved class of CAMs involved in a variety of biological processes, including synaptic regulation. In mammals, this family contains two members, IgSF9 and IgSF9b, that share 38% primary amino acid sequence homology (Hansen and Walmod, 2013). These proteins belong to the neural CAM subfamily within the IgSF of CAMs and are typified by two fibronectin-type three repeat domains and five Ig-like domains in their extracellular portions (Crossin and Krushel, 2000; Hansen and Walmod, 2013). Despite this homology, *in vitro* models suggest that although these IgSF members both localize to GABAergic synapses, IgSF9b predominantly populates inhibitory synapses onto interneurons, rather than pyramidal cells, as was reported with IgSF9 (Mishra et al., 2014; Woo et al., 2013). Additionally, an evolutionarily conserved drosophila cell adhesion protein (termed Borderless) belonging to the IgSF9 subfamily was found to regulate the transport of synaptic vesicle components to axon terminals in a subset of fly visual system neurons. This trafficking also required the presence of Borderless both pre- and postsynaptically, exemplifying a precise mechanism by which an IgSF9 CAM regulates synaptic homeostasis (Shaw et al., 2019). These insights garnered from closely related IgSF members provide additional context for the studies specific to IgSF9b conducted within the last decade.

Woo et al. observed that IgSF9b exhibits homophilic adhesion but does not appear to associate with other adhesion molecules (Woo et al., 2013). However, this finding was recently challenged by a high-throughput IgSF protein-protein interaction screen, which

discovered a novel interaction between IgSF9b and the cell adhesion molecule NEGR1 (Wojtowicz et al., 2020). There are no available data regarding the significance of this interaction, and therefore, this review will focus on IgSF9b through a homophilic lens. Interestingly, immunostaining assays in hippocampal cell culture revealed that IgSF9b is more highly expressed in interneurons compared to pyramidal cells and that it colocalized with inhibitory, but not excitatory, post-synaptic markers (such as PSD-95, vGlut1, and Shank). Protein expression was distributed to both somatic and dendritic compartments of the dissociated neurons in culture. IgSF9b is also reportedly expressed in axons, distally from the soma, and interacts with Prickle2 to control the positioning of AnkG within the axon initial segment in hippocampal cell cultures (Chowdhury et al., 2020). These findings indicate that IgSF9b is localized to multiple synaptic compartments within neurons - either somatic, dendritic, or axonic. IgSF9b was also unable to induce clustering of the inhibitory post-synaptic scaffolding protein gephyrin, suggesting that it cannot independently mediate inhibitory synapse formation (Woo et al., 2013). Taken together, these initial findings indicate that IgSF9b may be more involved in the maintenance and maturation of inhibitory synapses rather than their initial formation.

The inhibitory post-synaptic density contains a network of proteins, including receptors, protein kinases, and scaffolding proteins, that interact to support synaptic function (Krueger-Burg et al., 2017). Woo et al. reported that IgSF9b localized to a subdomain of the inhibitory synapse separate from the signaling-associated, gephyrin/$GABA_A$ receptor-containing domain. This finding was significant because it provided evidence that IgSF9b functions in a subsynaptic domain distinct from the receptor-rich domain, and perhaps adopts a structural, stabilizing role at inhibitory synapses. To provide more context for this finding, the authors sought to identify the protein-interaction mechanism by which IgSF9b fits into the inhibitory postsynaptic density (PSD). Via binding with Synaptic Scaffolding Cell Adhesion Molecule (S-SCAM, also known as MAGI-2), the intracellular domain of IgSF9b is anchored to the inhibitory post-synaptic density. Neuroligin 2 (Nlgn2), another CAM that localizes specifically to inhibitory synapses, also associates with S-SCAM, albeit at a protein domain distinct from IgSF9b, to form a ternary complex, as illustrated in Figure 1. Additionally, clustering of IgSF9b can be induced in the presence of S-SCAM in HEK293T cells, and in the presence of S-SCAM, IgSF9b can drive aggregation of Nlgn2, and vice versa (Woo et al., 2013). This suggests that S-SCAM possesses an organizing capacity to localize the clustering of IgSF9b with other inhibitory synaptic proteins (Woo et al., 2013). However, S-SCAM is not exclusively found at inhibitory synapses but is also known to regulate AMPA receptor levels and provide a scaffold for N-methyl D-aspartate (NMDA) receptors and neuroligin 1 at excitatory synapses (Sumita et al., 2007; Zhang et al., 2015). Therefore, S-SCAM is capable of bridging adhesion and PSD complexes across functionally distinct synapse types, including those containing IgSF9b.

From a functional standpoint, disruption of IgSF9b expression results in inhibitory synaptic deficits. Short hairpin (sh) RNA-mediated knockdown of IgSF9b in a subset of cultured hippocampal neurons resulted in a significantly decreased number of inhibitory synapses onto transfected interneurons. Reductions in inhibitory synapse numbers were also observed in transfected pyramidal cells, but the effect did not reach statistical significance (Woo et al., 2013). Importantly, the excitatory synapse number was not affected. Functionally, shRNA

knockdown also led to a decreased frequency of miniature inhibitory but not excitatory post-synaptic currents (mIPSCs) in interneurons. It should be emphasized that since these measures were collected from cells transfected with the IgSF9b knockdown construct, they are more indicative of the postsynaptic effects of IgSF9b dysfunction. Taken together, these results from cell culture studies suggest that IgSF9b is predominantly localized to inhibitory synapses on inhibitory neurons and is important for their maintenance, but not their *de novo* formation. This finding is significant, placing IgSF9b among the group of CAMs selectively present at inhibitory synapses; the others being Nlgn2, dystroglycan, and slitrk3 (Krueger-Burg et al., 2017). A caveat to these experiments is that they were conducted in developing neurons *in vitro*, rather than adult tissues, and IgSF9b may have heretofore undiscovered roles in neurodevelopment, a notion that will be discussed in future sections. Findings from animal models expound upon these cell culture studies to characterize the *in vivo* role of IgSF9b in inhibitory circuits.

2.2. In Vivo Findings

Current *in vivo* studies of IgSF9b provide more context for its implications in psychiatric disorders and neural circuit development. Babaev et al. sought to elucidate the role of IgSF9b in anxiety-like behaviors in rodents (Babaev et al., 2018). To this end, the authors employed a whole-organism IgSF9b knockout (KO), assaying anxiety-like behaviors and electrophysiological properties specifically within amygdala anxiety circuitry. Behaviorally, one of the most striking findings was that IgSF9b knockout animals displayed an anxiolytic phenotype. These mutants spend more time in the center of the open field (OF), which is typically considered anxiogenic due to the lack of shadows that are present on the walls of the enclosure (Seibenhener and Wooten, 2015). Additionally, IgSF9b KO mice spent more time, traveled farther, and more frequently ventured into the open arms of the elevated plus maze (EPM) compared to wild-type littermates (Babaev et al., 2018). These effects were not due to an overall impact on locomotor behavior and were therefore considered relevant to the animal's affective state in the context of these tasks.

While the EPM and OF have historically been used to detect anxiety-like behavior in rodents (Walf and Frye, 2007), these tasks may also be conceptualized as an assay of approach-avoidance behavior (La-Vu et al., 2020). In this framework, IgSF9b KO mice may be thought of as approach-biased, which is likely due to perturbation across enumerable brain circuits involved in gating exploratory behavioral responses in the face of perceived threat (Adhikari, 2014). Given the functional relevance of the amygdala to anxiety-related behavior, Babaev et al. focused their further manipulations on this region. Considering the rodent amygdala is not a monolithic structure, the authors explored the effects of IgSF9b knockdown across multiple subregions, including the lateral, basal (BA), central lateral, and central medial (CeM) partitions. Electrophysiological recordings from IgSF9b knockout animals in the CeM, a region composed almost entirely of inhibitory neurons, yielded an increase in the frequency of mIPSCs (Babaev et al., 2018). This is in direct contrast to the cell culture studies, in which IgSF9b knockdown resulted in a decrease in mIPSCs frequency (Woo et al., 2013). Further, recordings from the BA yielded no significant changes in inhibitory current amplitude or frequency. These conflicting findings across

electrophysiological studies indicate that the circuit effects of IgSF9b dysfunction are likely brain region and cell type-specific.

These *in vivo* studies attest to the region-specific function of IgSF9b. Interestingly, targeted knockdown of IgSF9b in the CeM during adulthood did not affect OF behavior, which suggests that loss of IgSF9b in other brain regions drove the anxiolytic effects observed in the KO model. Another possibility is that IgSF9b is developmentally regulated in the CeM, such that perturbation during the adult stage does not give rise to detectable anxiolytic phenotypes (Babaev et al., 2018). Also, given that IgSF9b KO did not affect inhibitory transmission in the BA, but led to an overall increase in the amount of cFos+ cells in this subregion after OF exposure, it is plausible that IgSF9b KO results in increased excitatory drive to the BA from other brain regions. Further investigation is needed to determine if this indeed is the case and to examine the circuit-based mechanisms by which IgSF9b dysfunction leads to behavioral changes.

Another more recent study identified a role for IgSF9b outside of the realm of anxiety behavior, focusing on its role in the development of the visual system. The role of sensory experience in shaping cortical circuits throughout development is a pertinent question in neuroscience research. Exactly how experience drives gene expression to mediate cortical maturation is not entirely known, although IgSF9b is reportedly involved in this process, at least in the visual system. Using single-nucleus RNA sequencing (RNA-seq), Cheng et al. examined gene expression in the mouse primary visual cortex across six postnatal developmental time points (Cheng et al., 2022). They found that the development of layer 2/3 neurons is highly sensitive to visual input and that some genes gradually increase their expression in these neurons in a manner that coincides with the critical period for the development of binocular dominance. Strikingly, one of these genes was IgSF9b, which showed low expression in layer 2/3 before eye opening but markedly increased after eye opening. Further, rearing mice in the dark resulted in greatly diminished IgSF9b expression in these neurons, and this effect was rescued when dark-reared mice were placed back in the light. In addition, IgSF9b KO resulted in decreased postsynaptic inhibitory markers in layer 2/3 of neurons, suggesting that the sensory experience-dependent expression of IgSF9b results in increased inhibition of these neurons (Cheng et al., 2022).

Spatial patterning of IgSF9b expression in layer 2/3 of V1 was also inversely related to expression of Mdga1, a cell surface protein found to inhibit Nlgn2-driven inhibitory synapse formation (Lee et al., 2013; Pettem et al., 2013). This is in line with the previous finding that Nlgn2 can drive the clustering of IgSF9b (Woo et al., 2013) and highlights that protein interactions between inhibitory synaptic adhesion molecules enable spatially defined expression at precise developmental time points. Finally, calcium imaging in postnatal day 36 IgSF9b KO mice revealed that this increased inhibition is necessary for the establishment of binocular dominance responses in layer 2/3 neurons (Cheng et al., 2022). These results indicate that IgSF9b expression can be regulated by sensory input in some cell types. Considering the importance of postnatal IgSF9b expression demonstrated by these studies, and the protracted expression patterns of IgSF9b in rodents and humans (Woo et al., 2013), IgSF9b may serve as a mediator of experience-dependent synaptic regulation outside of the visual system, contributing to sculpting inhibitory circuits in response to a range of

environmental stimuli. Future studies are necessary to interrogate the role of IgSF9b in the proper development of inhibitory circuits in brain regions relevant to psychiatric disorders.

3. IgSF9b Implications in Psychiatric Disorders

3.1. Psychiatric disorders as synaptopathies

As previously touched upon, IgSF9b gene mutations have been linked to psychiatric disorders, including SZ and MDD (Schizophrenia Working Group of the Psychiatric Genomics, 2014; Shyn et al., 2011). Many psychiatric disorders are known to involve disruptions in synaptic homeostasis and can therefore be conceptualized as synaptopathies (Gao and Penzes, 2015; Gao et al., 2022; Howes and Onwordi, 2023; Trubetskoy et al., 2022). Cell adhesion molecules generally, and mutations in their respective genes, have previously been implicated in the pathophysiology of psychiatric disorders (Betancur et al., 2009; Jaudon et al., 2021; Mackowiak et al., 2014; Mizutani et al., 2021; Nomura et al., 2021; O'Dushlaine et al., 2011), highlighting the need to develop a better understanding of how disrupted cell adhesion processes contribute to pathogenesis. Although there are no current studies that link mutations in the IgSF9b gene to synaptic deficits in humans, we postulate that it is part of a larger set of psychiatric risk genes that, when perturbed, result in synaptic impairments and disease phenotypes (Forsyth et al., 2020; Hall et al., 2015). Considering the preclinical evidence supporting IgSF9b's role in inhibitory synaptic function, we present broader evidence linking synaptic dysfunction to psychiatric disorders, focusing primarily on SZ. These findings illustrate how IgSF9b could play a role in psychiatric disease etiology.

Threats to neurobiological function may affect distinct cell types, circuits, and/or neuromodulatory systems at key maturational time points to drive SZ pathology. Of these threats, two primary observations pertaining to inhibitory synaptic regulation are highly relevant to IgSF9b. The first is that there are consistent reports of deficits in markers of cortical GABAergic transmission and interneuron function in SZ [reviewed in (Dienel and Lewis, 2019)]. Namely, SZ patients show marked reductions in expression of GABA synthetic enzyme GAD67 in the prefrontal cortex (PFC), reduced $GABA_A$ receptor subunit expression, and aberrant expression of cortical interneuron markers including PV, SST, and CCK (Glausier et al., 2014; Hashimoto et al., 2008). Additionally, a compelling study conducted in cortical interneurons derived from induced pluripotent stem cells of SZ subjects revealed significant reductions in inhibitory synaptic markers including GAD67, Nlgn2, and gephyrin (Kathuria et al., 2019). These clinical findings support the notion that disruptions in inhibitory synaptic signaling are a core component of SZ pathology. Thus, there is a dire need to understand the genetic mechanisms that contribute to this pathological domain.

A second salient point is the demonstrable increase in inhibitory synaptic innervation that occurs in the PFC throughout adolescence and early adulthood (Insel, 2010; Lewis and Levitt, 2002). This observation suggests that developmentally programmed processes that orchestrate synaptic formation, maintenance, and pruning are disrupted in SZ, but the exact genetic mechanisms that might lead to this disruption - especially for inhibitory synapses - are not well understood. This feature of SZ pathology is intriguing in the case

of IgSF9b, given that its expression in the brain appears to increase during late postnatal development (Woo et al., 2013), and it is heavily involved in inhibitory synaptic maturation and maintenance. Future studies are needed to understand how developmentally regulated synaptic events are disrupted in psychiatric disorders such as SZ. Disruptions in synaptic architecture are also observed in other common psychiatric disorders with which IgSF9b has been associated, such as MDD and anxiety.

Similar to the findings in patients with SZ, studies of humans with MDD and rodent models of depression reflect a decreased number of synapses and a decrease in GABAergic interneurons in the PFC (Duman, 2014; Duman and Aghajanian, 2012). Anxiety disorders have also been linked to decreased inhibitory signaling (Gao et al., 2022), and IgSF9b mutations have been shown to lead to altered anxiety-related behavior in mice (Babaev et al., 2018). The importance of IgSF9b in neurological disorders cannot be understated, as mutations in this gene have been associated with a diverse array of conditions, across numerous studies.

3.2. Genetic Evidence on IgSF9b

From a genetics perspective, single-nucleotide polymorphisms (SNPs) in the IgSF9b gene locus have been associated with a plethora of neurological disorders (**detailed in** Table 1). In the NHGRI-EBI GWAS Catalog, IgSF9b SNPs have also been associated with traits including ‘Educational Attainment’, ‘Body Fat/BMI’, and ‘Taste Preference’ not pertaining to a specific disorder (Sollis et al., 2023). Additionally, studies have implicated IgSF9b in transcription regulation, non-neurological, and evolutionary domains (Gulsuner et al., 2020; Kiselev et al., 2022; Wang et al., 2021; Yoshihara et al., 2014; Zhang et al., 2020). While IgSF9b genetic variants are associated with many neurological disorders, the predominant disease link is with SZ. Of these variants, the rs75059851 SNP is the most frequently detected, and has been specifically linked with negative symptoms of SZ (Fabbri and Serretti, 2017). Importantly, negative symptoms are typically more resistant to treatment and more chronically debilitating. Thus, closer inspection of this IgSF9b variant is warranted from both biological and clinical perspectives.

The major allele for this SNP contains an adenine residue, while guanine is found in the minor allele. Notably, this polymorphism occurs not in the coding region of IgSF9b, but within an intron, suggesting it may dysregulate pre-mRNA splicing (Pagani and Baralle, 2004). Intronic variants may be characterized as either proximal to the splice junction boundary, or deep, located distally from the splice site. While both variant types can result in pathological consequences in gene function, deep intronic variants oftentimes result in pseudo-exon inclusion, which is characterized by the inclusion of pre-mRNA sequences that are ordinarily removed before translation (Vaz-Drago et al., 2017). The inclusion of this so-called pseudo-exon may lead to a premature stop codon and degradation of the mRNA transcript via nonsense-mediated mRNA decay (Popp and Maquat, 2013). Rs75059851 is a deep intronic variant, however, these effects are merely conjectural, as the *in vivo* effects of the rs75059851 variant on IgSF9b expression are currently unknown.

Another perplexing aspect of this SNP is that the major allele is the variant associated with SZ, rather than the minor one. This suggests that the minor allele may serve some

protective benefit in the presence of other disease-associated factors. Thus, it is not currently known whether IgSF9b in these individuals is upregulated, downregulated, or affected in some other way. This is the case for many psychiatric disease-associated SNPs; their functional relevance is not known, but rather an association between genotypes and symptoms is identified without much insight into the pathological mechanism that lies in between. Interestingly, one study found that among the variants identified in the largest SZ GWAS study to date (Trubetskoy et al., 2022), IgSF9b was linked to 7 noncoding variants, which is the most of any gene in the study (Wu et al., 2023). With the advent of high-precision genome editing tools like CRISPR/Cas9, future research into SNP-specific disease mechanisms is achievable and can provide insight into how distinct genetic variation affects neural function *in vitro* and *in vivo*. Besides alterations in the genomic sequence of IgSF9b, it is also important to consider gene interactions that may influence IgSF9b function.

Given that GWAS has identified hundreds of genes relevant to psychiatric disorders, it is plausible that there is overlap in the disruptions of gene networks that subserve common neurological functions. The known interaction partners of IgSF9b are Nlgn2 and S-SCAM, which together form a ternary complex in the PSD of the GABAergic synapse (Woo et al., 2013). Notably, all of these proteins have been linked to disease, and both S-SCAM (Koide et al., 2012; Singh et al., 2022) and Nlgn2 (Parente et al., 2017; Sun et al., 2011) have been linked to psychiatric disorders including SZ and ASD. This is intriguing given that SZ and ASD are considered polygenic disorders, such that disruption of any of numerous genes can potentially lead to common disease phenotypes. Indeed, a current goal of psychiatric disease research is to understand how the multiplicity of mutations across thousands of genes potentiates overlapping perturbations of behavior and cognition. In the case of IgSF9b, it appears that mutations in any member of its ternary complex may lead to disease phenotypes (Shin et al., 2020; Zhang et al., 2015), providing an example of how disruption on multiple fronts may converge to impair GABAergic synapse function. These findings also present a rationale to explore therapeutic options for the restoration of inhibitory synaptic function that is disrupted in psychiatric disorders.

3.3. Therapeutic Implications for IgSF9b

In terms of therapeutics, many options have been studied and targeted to promote excitatory synaptic function (i.e., spinogenesis) and/or inhibitory neuronal connectivity (Chamberlin et al., 2023). For example, ketamine, an N-methyl D-aspartate (NMDA) receptor antagonist increasing in popularity for the treatment of MDD, has been shown to increase the number and function of dendritic spines (Ardalan et al., 2017; Li et al., 2010). Considering the prevalence of GABAergic deficits in psychiatric disorders previously discussed, targeting pharmacological treatment to components of inhibitory synapses may also provide therapeutic benefits (Lewis et al., 2005). Preclinical models and basic research can provide insight into the disease mechanisms underlying the consequences of disruption of inhibitory synaptic organizers like IgSF9b. Further inquiry into the precise synaptopathies impacting various psychiatric disorders - whether they affect excitatory, inhibitory, or both - is necessary to provide more individualized therapeutics to individuals struggling with these conditions. Ultimately, because many psychiatric disorders are typified as polygenic and

often do not arise from single gene mutations, understanding the convergences in nervous system dysfunction caused by a plethora of genetic and environmental threats is paramount.

4. Understanding the role of IgSF9b in development and its expression between cell types

A prevailing view in the age of modern neuroscience is that patterns of gene expression across cell types underlie their developmental trajectories and mature function. This notion is particularly relevant to IgSF9b, given that currently published work suggests that this gene shows both cell type and developmental specificity in its expression patterns; Woo et al. showed that IgSF9b protein expression in the brain peaks at around three postnatal weeks in rats. Based on findings from Woo et al. and Babaev et al., it appears IgSF9b is predominantly expressed in interneurons to regulate inhibitory-inhibitory synaptic connections. However, the findings from Cheng et al. suggest that this cell type specificity may not generalize across brain regions, as experience-dependent changes in IgSF9b expression were detected in layer 2/3 glutamatergic cells of the visual cortex (Cheng et al., 2022). Together, these findings suggest that IgSF9b is both developmentally regulated and differentially expressed depending on the brain region and the cell types present therein. Therefore, future research toward understanding the role of IgSF9b should probe its function in a region and cell-type-specific manner. To help provide insight into this knowledge gap, we compiled publicly available IgSF9b expression data, from both humans and mice (Miller et al., 2014; Yao et al., 2021c). We believe these data provide clues for future inquiry into the role of IgSF9b.

A pertinent question related to IgSF9b function is whether it is developmentally regulated across brain regions in humans. It is tempting to consider that IgSF9b expression across development correlates with inhibitory synapse maintenance dynamics that are necessary for the proper maturation of neural circuits. To gain insight into this question and to identify trends in IgSF9b expression across human brain development, we explored bulk RNA-Seq data from the BrainSpan initiative (brainspan.org). In these studies, RNA from multiple brain regions (8-16, depending on the developmental stage) was extracted from healthy donor samples ranging from fetuses of 4 post-conceptional weeks to adults 60 years or older to provide genome-wide expression data of over 50,000 genes.

We first sought to determine if IgSF9b expression varies across brain regions in adults. This analysis revealed that the cerebellar cortex exhibits the greatest normalized expression (in units of transcripts per kilobase million (TPM)), followed by prefrontal and sensory/motor cortical regions (find regional categorizations in supplement) (Figure 2A). This result is compatible with the observation that the cerebellar cortex is comprised predominantly of inhibitory cell types, including Purkinje cells, stellate cells, and basket cells, that contact each other via inhibitory synapses (Prestori et al., 2019). While the cerebellum has a longstanding role in motor control and motor learning, recent studies suggest that the cerebellum additionally plays a role in emotional processing and cognition (Adamaszek et al., 2017; Schmahmann and Caplan, 2006). Expression in the adult PFC raises implications

about the role of IgSF9b in the prefrontal cortical regions that are disrupted in psychiatric disorders.

We then turned to developmental data to understand IgSF9b expression trends. First, we averaged expression across all brain regions for each donor, computing an IgSF9b expression value for each donor (Figure 2B). However, given that IgSF9b appears to be expressed in some brain regions more than others, we stratified developmental expression into regional categories to determine if any category shows significant deviations from one developmental time point to the next (Figure 2C). Again, the cerebellar cortex was unique, displaying a marked increase in expression during the postnatal period. Surprisingly, expression in subcortical regions (particularly the striatum) displayed a marked increase during the early prenatal period. Finally, since frontal cortical regions are highly implicated in psychiatric disorders, and because more nuanced changes in expression may be obscured due to scaling in Figure 2C, we explored expression dynamics across these brain regions (Figure 2D). These data suggest that IgSF9b expression is enhanced early after birth, and then again during adulthood, which begs the question as to whether IgSF9b is important for proper maturation of the circuits in these regions later in life. The BrainSpan data reveals developmental changes in IgSF9b expression, which are often brain-region specific. To investigate IgSF9b expression on a single-cell level, we utilized RNA-Seq data derived from the murine neocortex and hippocampus.

For these exploratory analyses, we endeavored to glean information regarding how different cell types express IgSF9b across brain regions. To accomplish this, we explored single-cell RNA-Seq data from mouse neocortex and hippocampus provided by the Allen Institute (Yao et al., 2021c). A key feature of this dataset is that cells across these regions were categorized based on their gene expression, forming a taxonomy of glutamatergic and GABAergic cell types. To get a better sense of IgSF9b on a single-cell level, rather than a cluster level, we explored the central tendency of IgSF9b expression across all cells within each region (Figure 3A). This analysis showed that IgSF9b is most highly expressed in the posterior parietal association area, followed by the visual cortex, the latter of which aligns with the studies of visual system development (Cheng et al., 2022). By and large, it appears IgSF9b expression is consistent across the cortex and hippocampus, at least in the adult mouse. In Figure 3B, normalized IgSF9b expression is represented for each of 388 transcriptomically determined cell types across all sequenced brain regions. These data show that IgSF9b is expressed not only in glutamatergic and GABAergic cell types but also in non-neuronal cells such as oligodendrocytes. Also of note is that glutamatergic cell type clusters appear to segregate into ‘high’ and ‘low’ expression patterns, which raises questions about which factors (such as inhibitory synaptic density or region-specific projection) make these ‘high’ expression cell clusters distinct.

Finally, we explored IgSF9b expression in three major inhibitory cell types: parvalbumin (PV), somatostatin (SST), and vasoactive intestinal polypeptide (VIP). These genes are considered markers of three cardinal classes of cortical inhibitory neurons that exhibit differential synaptic targeting along the axo-somato-dendritic axis of postsynaptic cells (Fishell and Kepecs, 2020). We compared IgSF9b expression in these cell type samples from all regions of the neocortex and hippocampus and found that VIP interneurons appear

to express higher quantities of IgSF9b than other inhibitory cell types (Figure 3C, 3D). This is particularly intriguing considering that VIP cells typically target other inhibitory cell types (particularly SST), to mediate disinhibition of pyramidal cell activity (Tremblay et al., 2016). This trend was consistent when these cells were filtered to include only those from the prelimbic and infralimbic cortices, representing the mouse mPFC, a region involved in top-down regulation of affective behavior (Anastasiades and Carter, 2021). The single-cell data suggest that among the major cortical interneuron classes, IgSF9b expression is highest in VIP+ cells, potentially due to their inhibitory synaptic targeting of GABAergic cells. The data also strongly suggest that IgSF9b is not solely found at these synapse types, considering many glutamatergic cell types also express IgSF9b. This discrepancy between the literature and the single-cell data may be due in part to the fact that most of the mechanistic experiments (Woo et al., 2013) were conducted in cell culture, a model that is subject to variation from *in vivo* assays.

5. Conclusions and Outstanding Questions

Our understanding of psychiatric disorders is greatly hindered by our incomplete comprehension of the precise mechanisms by which neurons across brain regions make connections to facilitate adaptive behavior. Canonically, inhibitory interneurons in the cortex and hippocampus are thought to gate the flow of information between brain regions by controlling the activity of long-range projections (Fishell and Kepecs, 2020). Therefore, it can be anticipated that genetic perturbation of any component of the inhibitory synapse would impair the proper regulation of this information flow and lead to maladaptive cognition and behavior. IgSF9b appears to be a clear example of this, but there are still many questions left unanswered, as listed in the outstanding questions (Box 1).

While the current literature supports the notion that IgSF9b is important for inhibitory synaptic maintenance, it has not been shown directly that IgSF9b regulates inhibitory synaptic persistence or transience *in vivo*. Given the expression dynamics of IgSF9b, a compelling notion is that IgSF9b is a mediator of inhibitory synaptic plasticity throughout postnatal brain development and is particularly important during critical period windows, wherein modulation of inhibitory wiring is essential for the establishment of adaptive circuits (Delevich et al., 2018). In terms of psychiatric disorders, dysregulated refinement of prefrontal cortical output due to improper establishment of inhibitory microcircuits in adolescence may result in cognitive and behavioral deficits (Klune et al., 2021; Lewis, 1997). Cheng et al. also provided evidence that IgSF9b expression correlates with visual sensory experience, suggesting that IgSF9b may mediate inhibitory synaptic plasticity at developmental critical periods across the brain in an experience-dependent manner (Cheng et al., 2022). Further studies are needed to assess the role of IgSF9b in affective behaviors relevant to psychiatric disorders and to delve deeper into the effects of region-specific or cell type-specific knockouts upon these behaviors. Studies of this nature will help to inform future therapeutic approaches for psychiatric disease and further our understanding of the role of cell adhesion molecules in the construction of functional brain circuits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ACA	Anterior cingulate cortex
AI	Agranular insular cortex
ALM	Anterolateral motor cortex
ASD	Autism spectrum disorders
AUD	Auditory cortex
BA	basal amygdala
CAM	Cell adhesion molecule
CB	Collybistin
CPM	Counts per million
CT	corticothalamic
DFC	dorsal frontal cortex
EPM	Elevated plus maze
ENTl	Lateral entorhinal area
ENTm	Meidal entorhinal area
FC	frontal cortex
FNIII	Fibronectin type three domain
GABA	Gamma amino-butyric acid
GU	Gustatory cortex
GWAS	Genome-wide association study
HIP	Hippocampus
IgSF	Immunoglobulin Superfamily

Ig	Immunoglobulin
IT	intratelencephalic
KO	Knockout
MDD	Major depressive disorder
mIPSC	Miniature inhibitory postsynaptic current
MFC	medial frontal cortex
Mop	Primary motor cortex
NP	near-projecting
OF	Open field
OFC	orbital frontal cortex
Oligo	Oligodendrocyte
ORB	Orbital cortex
PB	PDZ-domain binding motif
PFC	Prefrontal cortex
PL-ILA	prelimbic & infralimbic cortices
PPP	Para, post and persubiculum
PT	pyramidal tract
PV	parvalbumin
PYLp	Posterior parietal association cortex
RNA-Seq	RNA Sequencing
RSP	Retrosplenial cortex
RSPv	Retrosplenial cortex (ventral)
S-SCAM	Synaptic scaffolding cell adhesion molecule
Sh	Short hairpin
SNP	Single-nucleotide polymorphism
SP	Singal peptide
SSp	Primary somatosensory cortex
SSs	Supplementary somatosensory cortex
SST	Somatostatin

SP	Subiculum & prosubiculum
SZ	Schizophrenia
TM	Transmembrane domain
TPE	Temporal association area, perirhinal and ectorhinal areas
TPM	Transcripts per kilobase million
VFC	ventral frontal cortex
VIP	Vasoactive intestinal polypeptide
VIS	Assorted visual areas
VISp	Primary visual area

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Box 1.

Outstanding Questions.

- What is the role of IgSF9b in sculpting functional inhibitory circuits in the adult brain?
  - Does IgSF9b play a role in the transience or persistence of inhibitory synapses *in vivo*?
  - What is its role in learning and memory, as well as social behavior and affective functions that are associated with psychiatric disorders?
- Do the neuronal cell types linked by IgSF9b vary across brain regions?
- What are the cell-autonomous or activity-dependent mechanisms that trigger the expression of IgSF9b?
- How does IgSF9b dysfunction influence the development of psychiatric symptoms?
  - What are the implications of the marked increase in IgSF9b expression during adolescent brain development?

Highlights

- IgSF9b is a high-risk gene associated with psychiatric disorders.
- IgSF9b is a cell adhesion molecule localized to inhibitory synapses in the brain.
- Our understanding of IgSF9b in cortical development remains limited.
- We explore the implications of IgSF9b dysfunction in rodents and humans using open-access gene expression databases.

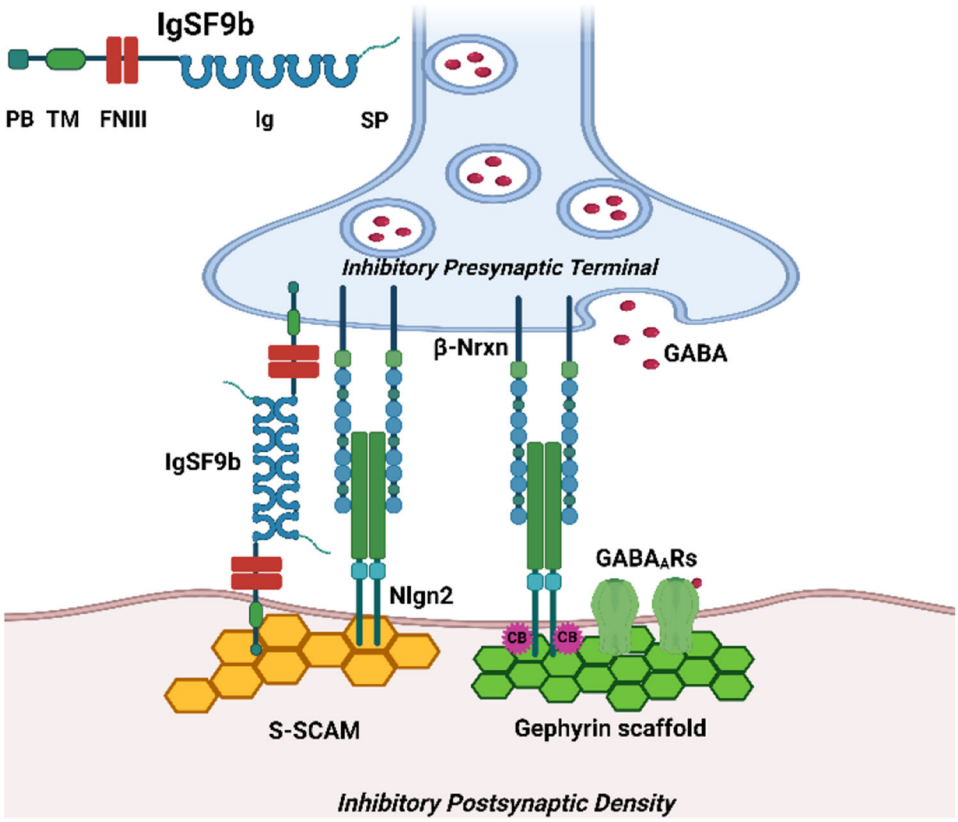

Figure 1. Proposed localization of protein IgSF9b at the inhibitory synapse.

Schematic of presynaptic inhibitory interneuron synapsing onto a postsynaptic cell. IgSF9b forms a ternary complex with the homodimer neuroligin 2-β-neurexin adhesion complex via S-SCAM at the inhibitory postsynaptic density. Also present are the core inhibitory postsynaptic density proteins gephyrin, collybistin, and $GABA_A$ receptors. Additionally, IgSF9b on the presynaptic cell can participate in homophilic binding with IgSF9b located on the postsynaptic ternary complex, mediating cell adhesion. IgSF9b protein domains, top right. PB, PDZ domain-binding motif; TM, transmembrane domain; FNIII, fibronectin type III domain; Ig, immunoglobulin domain; SP, signal peptide; Nlgn2, neuroligin 2; CB, collybistin.

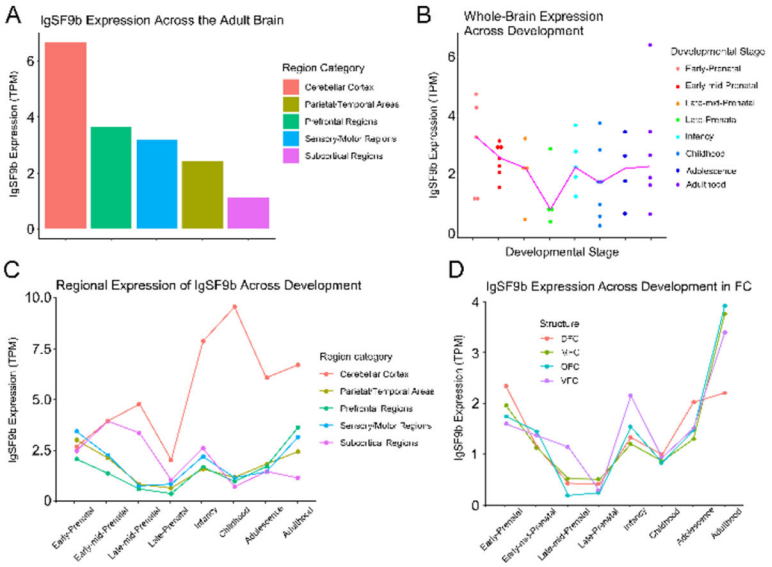

Figure 2. Representation of IgSF9b expression throughout human brain development from the BrainSpan RNA-seq dataset.

Data processing and analysis, including region and developmental stage categories, are defined in supplementary information. **A)** Adult brain IgSF9b expression in general region categories. **B)** Developmental timeline of whole-brain IgSF9b expression. Each point represents the average IgSF9b expression across all regions for an individual donor. **C)** Developmental timeline of IgSF9b expression in frontal cortical regions. Points represent the average expression values of samples at each developmental stage. **D)** IgSF9b expression for each region category across development. FC, frontal cortex; DFC, dorsal frontal cortex; MFC, medial frontal cortex; OFC, orbital frontal cortex; VFC, ventral frontal cortex; TPM, transcripts per kilobase million.

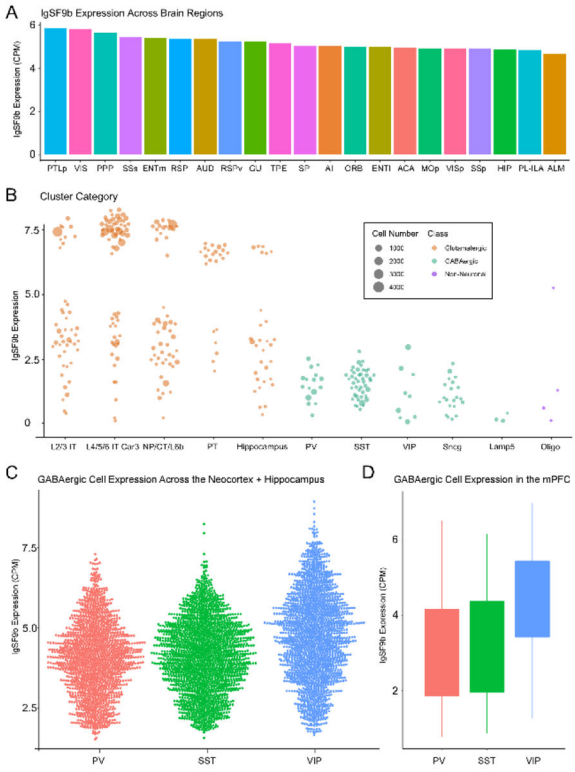

Figure 3. Allen Institute Adult Mouse Whole Neocortex and Hippocampus Single-Cell RNA-Seq Data Reveals IgSF9b expression in diverse brain regions and cell types.

A) IgSF9b transcript abundance through cortical and hippocampal regions. Region abbreviations are defined in supplementary information. **B)** IgSF9b expression in over 300 cell type clusters, as defined by Yao et al. 2021. Cell clusters are grouped into general categories on the x-axis and sized based on the number of cells used to calculate the IgSF9b expression value. More information regarding categorization and cluster expression values can be found in Supplementary Information. **C)** Single-cell expression of IgSF9b in three major GABAergic interneuron subtypes throughout the neocortex and hippocampus. **D)** IgSF9b in major GABAergic interneuron subtypes in the mPFC (including prelimbic and infralimbic cortices). ACA, Anterior cingulate cortex; AI, Agranular insular cortex; ALM, Anterolateral motor cortex; AUD, Auditory cortex; CT, corticothalamic; CPM, Counts per million; ENTl, Lateral entorhinal area; ENTm, Meidal entorhinal area; GU, Gustatory cortex; HIP, Hippocampus; IT, intratelencephalic; MOp, Primary motor cortex; NP, near-projecting; Oligo, Oligodendrocyte; ORB, Orbital cortex; Para, post and persubiculum; PL-ILA, prelimbic & infralimbic cortices; PT, pyramidal tract; PYLp, Posterior parietal association cortex; PV, parvalbumin; RSP, Retrosplenial cortex; RSPv, Retrosplenial cortex (ventral); SSp, Primary somatosensory cortex; SSs, Supplementary somatosensory cortex; SP, Subiculum & prosubiculum; SST, Somatostatin; TPE, Temporal association area, perirhinal and ectorhinal areas; VIP, Vasoactive intestinal polypeptide; VIS, Assorted visual areas; VISp, Primary visual area.

Table 1.

Summary of IgSF9b SNPs associated with neurological disorders

SNP ID	Trait Associations and Corresponding Studies		Demographics of Study Population	Variant Type
rs75059851 (A>G)	**Schizophrenia**	(Cross-Disorder Group of the Psychiatric Genomics Consortium. Electronic address and Cross-Disorder Group of the Psychiatric Genomics, 2019)	European ancestry	Intronic
		(Goes et al., 2015)	Ashkenazi Jewish ancestry	
		(Ikeda et al., 2019)	East Asian and European Ancestry	
		(Li et al., 2017)	East Asian (Chinese) and European Ancestry	
		(Schizophrenia Working Group of the Psychiatric Genomics, 2014)	East Asian and European Ancestry	
		(Wu et al., 2020)	Meta-analysis, varying ancestries	
rs4936215 (A>G)	**Schizophrenia**	(Jaffe et al., 2020)	Majority European ancestry	Intergenic
		(Pardinas et al., 2018)	European Ancestry	
		(Trubetskoy et al., 2022)	European, East Asian, African, Latino and Afro-Caribbean Ancestry	
		(Wang et al., 2022)	European Ancestry	
	Multiple traits (ASD, Schizophrenia)	(Peyrot and Price, 2021)	European Ancestry	
rs4937860 (A>G)	**Cognitive function**	(Lee et al., 2018)	European ancestry, all studies	Intronic
		(Demange et al., 2021)		
	Insomnia	(Watanabe et al., 2022)		
rs73034263 (C>G)	**Generalized Anxiety Disorder**	(Wendt et al., 2022)	European ancestry, all studies	Intronic
	Neuroticism	(Nagel et al., 2018a)		
		(Nagel etal., 2018b)		
rs12273435 (G>A)	**Cognitive function**	(Lee et al., 2018)	European ancestry – All studies	Intronic
	Insomnia	(Watanabe et al., 2022)		
	Multiple traits (ADHD, substance abuse, antisocial behavior)	(Karlsson Linner et al., 2021)		
rs167915 (A>T)	**Neuroticism**	(Kichaev et al., 2019)	European ancestry – All studies	Intronic
		(Nagel et al., 2018a)		
	Worry	(Nagel et al., 2018b)		
rs3802920 (G>A,C,T)	**Parkinson's disease**	(Ghanbari et al., 2016)	European ancestry – All studies	Intronic
		(Nalls et al., 2019)		
	Multiple traits (Parkinson's Disease and Schizophrenia)	(Smeland et al., 2021)		
rs3802921 (T>C)	**Parkinson's disease**	(Ghanbari et al., 2016)	European ancestry – Both studies	3' UTR

SNP ID	Trait Associations and Corresponding Studies		Demographics of Study Population	Variant Type
	Multiple traits (Parkinson's Disease and Schizophrenia)	(Smeland et al., 2021)		
rs3802924 (A>C)	**Multiple traits**	(Rao et al., 2022)	European Ancestry	Regulatory region variant
	Schizophrenia	(Lam et al., 2019a)	East Asian and European Ancestry	
rs4936216 (C>T)	**Multiple traits (Schizophrenia, intelligence, self-reported educational attainment)**	(Lam et al., 2019b)	European ancestry – Both studies	Intergenic
	Schizophrenia	(Yao et al., 2021a)		
rs329648 (T>A,C)	**Parkinson's disease**	(Chang et al., 2017) (Nalls et al., 2014)	European ancestry – Both studies	Regulatory region variant
		(Ghanbari et al., 2016)		
rs10894768 (C>A,G,T)	**Multiple sclerosis**	(Gil-Varea et al., 2018)	MS patients with either benign or aggressive disease phenotypes	Synonymous variant
rs11223656 (T>A)	**Schizophrenia**	(Wu et al., 2020)	Meta-analysis	Intergenic
rs502834 (G>A,T)	**Schizophrenia**	(Periyasamy et al., 2019)	South Asian (Indian) and European Ancestry	Intronic
rs595986 (A>G)	**Schizophrenia**	(Trubetskoy et al., 2022)	European, East Asian, African, Latino and Afro-Caribbean Ancestry	Synonymous variant
rs329647 (G>A,C)	**Schizophrenia**	(Trubetskoy et al., 2022)	European, East Asian, African, Latino and Afro-Caribbean Ancestry	Regulatory region variant
rs329674 (A>G,T)	**Bipolar disorder**	(Ikeda et al., 2018)	East Asian (Japanese) and European Ancestry	3' UTR
rs329640 (A>G)	**Major Depressive Disorder**	(Shyn et al., 2011)	European ancestry - SNP found in males, specifically	Intronic
rs12804787 (A>G)	**Insomnia**	(Watanabe et al., 2022)	European ancestry	Intronic
rs329664 (G>C,T)	**Insomnia**	(Watanabe et al., 2022)	European ancestry	Intergenic
rs329672 (C>G,T)	**Multiple traits (ADHD, ASD, intelligence)**	(Rao et al., 2022)	European ancestry	Intronic
rs561561 (A>T)	**Migraine disorder**	(Gormley et al., 2016)	European ancestry	Intergenic