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Unraveling the enigma of mental disorders: a genetics-first approach and the role of mouse models based on rare disease-susceptible genome variants

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ABSTRACT

Mental disorders are a major global cause of disability that involve significant disturbances in thinking, emotional regulation, or behavior. The pathogenesis of these illnesses is complicated by their obscure nature and lack of biological markers. A genetics-first approach has been proposed to address this complexity. This approach associates clinical phenotypes with disease-susceptible genomic variants, such as copy number variations and single nucleotide variants. These rare variants significantly affect disease development and are thus crucial for assessing the effects of specific variants on disease and in determining the underlying biological mechanisms. In particular, mouse models that reflect these variants are instrumental in defining the causal relationships between genetic variants and disease-relevant phenotypes. Recent studies have highlighted the importance of sensory information processing in humans and mice. Advanced technologies that are valuable in unraveling the neural circuit mechanisms of these phenotypes include optogenetics and in vivo 2-photon imaging. Furthermore, mouse models can guide the integration of findings from patients and induced pluripotent stem cells, supporting a multidimensional approach to understanding the pathophysiology of mental disorders. In this review, we briefly discuss the utility of mouse models in a genetics-first approach to elucidate the pathophysiology of mental disorders. We also present examples of our mouse models based on rare disease-susceptible variants.

Keywords: genetic-first approach, mouse models, rare disease susceptible variants, sensory processing

Abbreviations:
CNVs: copy number variations
iPSCs: induced pluripotent stem cells
SCZ: schizophrenia
ASD: autism spectrum disorder
22q11.2DS: 22q11.2 deletion syndrome
V1: primary visual cortex

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INTRODUCTION

The World Health Organization states that mental disorders have devastating rates of prevalence, mortality, morbidity, and disability and reduce the average life expectancy by 7–24 years.[1,2] As of 2019, mental disorders rank as the second leading cause of life disability worldwide, including in Japan, measured in years lived with disability. The limited efficacy of currently available treatments, which are effective in half of the patients,[3] exacerbates this situation.

The elusive nature of mental disorders presents a major obstacle to finding more effective treatments. Mental disorders lack specific biological markers, and their clinical diagnoses remain heterogeneous. Furthermore, they are characterized by a multifactorial etiology, involving a complex interplay of genetic, environmental, and neurobiological factors. This complexity makes establishing a clear link between the cause and onset or progression of the disease difficult.

A genetics-first approach has been proposed as an attempt to address this challenge.[4] By linking disease-susceptible genome variants to phenotypes, this approach builds a more biologically based framework for understanding these disorders. Copy number variations (CNVs) and single nucleotide variants (SNVs), rare susceptibility variants that significantly affect disease development, are important candidate markers in assessing the effect of a specific variant and psychiatric symptoms.[5]

This approach uses various methods and resources, including patient data, induced pluripotent stem cells (iPSCs), and mouse models, in determining the biological mechanisms underlying specific variants and phenotypes. However, none of these methods can comprehensively capture or recapitulate the process of disease development and onset. Mouse models are a valuable resource that can complement and combine findings from other types of resources. They provide a platform for studying chronological disease progression and allow the exploration of behavioral phenotypes, neuronal circuits, and causal relationships at a depth not feasible in human patients.[6]

Recent studies have highlighted the importance of atypical sensory information processing in patients with mental disorders[7,8] that may be related to psychiatric symptoms, such as delusions or hallucinations,[9-11] but which are difficult to evaluate directly in mouse models.

In this review, we briefly examine the role of mouse models in elucidating the pathophysiology of mental disorders, specifically focusing on neural circuit mechanisms underlying atypical sensory information processing. We also present our established mouse models.

RARE DISEASE-SUSCEPTIBLE GENOME VARIANTS

The significance of heredity in mental disorders has been recognized for over a century since Emil Kraepelin's[12] seminal work. Advances in genomic analysis technology have helped expand the body of evidence linking specific genomic variants to the development of mental disorders.[13] Genome-wide association studies of psychiatric traits have produced numerous discoveries regarding genetic risk variants and polygenic risk prediction.[14] Many mental disorders result from the complex interplay of numerous genetic factors, each of which exerting a relatively small effect on disease susceptibility. However, a distinct subset of mental disorders exhibits a limited population frequency of genetic variants with larger effect sizes, namely, severe early-onset neuropsychiatric disorders like autism spectrum disorder (ASD) and schizophrenia (SCZ).[15,16] These rare disease-susceptible variants, including CNVs and SNVs, are of significant interest in unraveling the complex genetic underpinnings of these disorders.

CNVs, which are segments of DNA (>50 bp) that can be either deleted or duplicated, are the most prevalent structural variations in the human genome. Large-scale case-control studies

Table Examples of psychiatric disease susceptible copy number variants

Genome variants	Associated neuropsychiatric disease	No. of protein-coding genes	Odds ratio
1q21.1 del	SCZ, ADHD, ID	20	8.35 [a]
1q21.1 dup	SCZ, ASD, ID, Epi	20	3.45 [a]
2p16.3 (NRXN1) del	SCZ, ASD, ID, Epi	1	9.01 [a]
3q29 del	SCZ, ASD, ID, BD	20	57.65 [a]
7q11.23 dup	SCZ, ASD, ID	24	11.35 [a]
15q11.2 del	SCZ, ASD, ID	5	2.15 [a]
15q11.2-q13.1 dup	SCZ, ASD, ID, Epi	14	13.2 [a]
15q13.3 del	SCZ, ASD, ID	8	7.52 [a]
16p11.2 dup	SCZ, ASD, ID, Epi, BD	27	11.52 [a]
22q11.2 del	SCZ, ASD, ADHD	44	28.27–∞ [a]
9q33.1 (*ASTN2*) del	ASD, ADHD, SCZ, BD	1–2	3.8 (BD) [b]
10q21.1 (*PCDH15*) del	ASD, SCZ, BD	1	3.8 (BD) [b]
11q14.1 (*DLG2*) del	SCZ, BD	1	19.1 [b]

SCZ: schizophrenia
BD: bipolar disorder
ASD: autism spectrum disorder
ADHD: attention-deficit hyperactivity disorder
Epi: epilepsy
ID: intellectual disability
[a, b] Odds ratio from Kato et al[19] (a) and Kushima et al[17] (b).

have robustly associated rare CNVs, particularly deletions, with mental disorders.[17,18] Examples of such disease-susceptible CNVs include 1q21.1, 2p16.3 (NRXN1), 3q29, 15q11.2, 16p11.2, and 22q11.2.[19,20] These and other CNVs have significant implications for understanding the pathophysiology of mental disorders. (Table)

SNVs are the single nucleotide variants that affect <1% of the population. Such single nucleotide changes have different consequences, including synonymous or nonsynonymous variants (eg, missense or nonsense). In addition, small insertions or deletions (indels) within the genome can disrupt the reading frame and cause errors in amino acid sequencing. Recent large-scale genetic analyses have revealed the substantial impact of rare de novo and inherited SNVs or small indels detected by whole-genome or whole-exome sequencing on the development of neuropsychiatric disorders.[15,21]

The characterization of mouse models based on these rare variants is critical for elucidating the pathophysiology of mental disorders and identifying novel drug targets. Rare variants can induce substantial functional changes in proteins, and various methods are being employed to elucidate the biological mechanisms of these disorders, specifically rare genetic variants.

GENETICS-FIRST APPROACH AND THE IMPORTANCE OF MOUSE MODELS

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders,[22] the current principal authority for diagnosing mental disorders, primarily relies on combinations of clinical symptoms. In this catalog of symptom combinations, each diagnosis affords multiple combinations of symptoms, resulting in diagnostic heterogeneity. Furthermore, individual clinical symptoms are often not specific to a mental disorder. In other words, common symptoms such as social withdrawal often appear in multiple mental disorders without exclusivity. This overlap of symptoms across different mental disorders complicates our understanding of the biological mechanisms underlying mental disorders.[23]

To address this problem, recent studies have adopted a genetics-first approach.[4,13] This approach establishes associations between specific genotypes and clinical phenotypes to provide a more biologically informed and precise framework for understanding and categorizing mental disorders. This is particularly valuable for understanding the molecular pathophysiology underlying these disorders, especially when managing rare disease-susceptible variants with significant effects on disease onset.[24]

Although different research resources based on the genetics-first approach are being used to study the pathophysiology of mental disorders, each has its advantages and limitations. Hence, to gain a comprehensive understanding of the biological mechanisms underlying these disorders, integrating findings from various sources, including mouse models is crucial.

Mouse models

Mouse models provide a valuable platform for exploring the effects of genetic variants on various biological processes at multiple levels. They enable us to examine the influence of the specific genetic variants on behavior, neural circuitry, cells, and molecules. The ability to study the entire developmental process from the prenatal to senescent stages is a major advantage of using mouse models. This feature is particularly useful in the study of mental disorders because symptoms are often not present at birth but tend to emerge during adolescence.[25] Various behavioral phenotypes can be studied using mouse models, including despair and anxiety-like behaviors and cognitive functions related to perception and memory. The mouse models also facilitate the assessment of relation between specific genetic variants and social functions that are significantly impaired in patients with mental disorders. Furthermore, mouse models enable the evaluation of causal relationships among molecular, cellular, and neural circuits and behavioral phenotypes, including procedures that are not feasible in human patients. Thus, findings from other resources can be tested in mouse models and examined for their biological mechanisms.

Human brain resources

Neurophysiological studies in patients, such as electroencephalography and functional magnetic resonance imaging (MRI), enable the examination of brain function and structure in living patients. However, they cannot establish a causal relationship between phenotype and anatomical or functional changes. Therefore, to elucidate the pathophysiology, translatable features must be identified and underlying biological mechanisms must be investigated in various studies including mouse models. Postmortem brain studies can illustrate the histopathological and cellular differences in diseases; however, they can be affected by comorbidities other than mental disorders and aging, and are inevitably affected by perimortem processes.

iPSCs

The study of patient-derived iPSCs provides insights into the effects of specific genetic variants

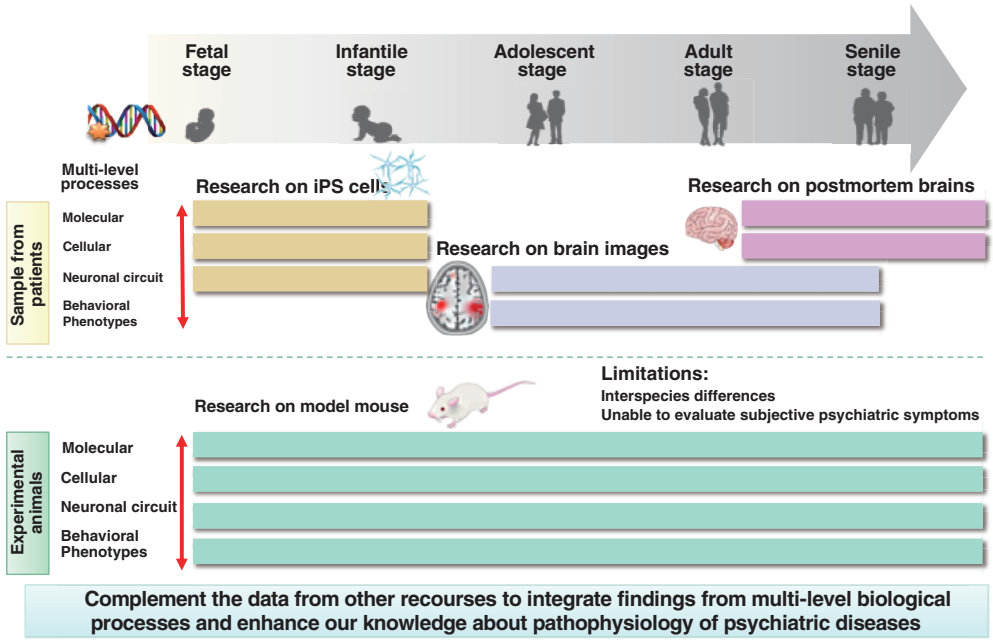

Fig. The role of mouse models in the research of psychiatric diseases
Mental disorders affect the lives of patients from fetal to senile stage. And their pathophysiology involves multi-level of biological processes, from molecular to individual behaviour. In order to elucidate the pathophysiology of mental disorders at each stage and each level, currently available models and samples from patients have their own strengths and weaknesses. Mouse models have unique strength in this aspect, that they enable us to study the entire disease process using the same model.
iPS cell: induced pluripotent stem cell

on molecular and cellular processes, particularly in the context of human brain development.[26] iPSCs and brain organoids allow us to observe the effect of specific variants on the physiological properties of cells. They also enable us to assess the causal effects of specific interventions. However, it is still difficult to fully recapitulate the complex microenvironment of the human brain.[27] In addition, iPSCs cannot establish a direct causal relationship between biological traits and individual behaviors, including psychiatric symptoms. These limitations underscore the importance of evaluating the findings from iPSCs in other resources, including mouse models.[28,29]

To unravel the intricate biological processes underlying these disorders, integrating findings from multiple levels and dimensions is essential. In this context, mouse models established to reflect that rare disease-susceptible variants have the same etiology as human patients can help to paint a comprehensive understanding of mental disorders. (Figure)

STUDIES USING MOUSE MODELS

Here, we provide examples of studies using mouse models to study mental disorders, with a focus on 22q11.2 deletion syndrome (22q11.2DS). 22q11.2DS is a neurogenetic disorder associated with high rates of SCZ and other mental disorders,[30] affecting 1 in 3,000–6,000 live births.[31] Several strains of mouse models for 22q11.DS, including our models reflecting the 22q11.2 deletion, have been generated.[32-35]

Evaluating the validity of mouse models for psychiatric diseases

The clinical diagnosis of mental disorders is not based on concrete biological markers; thus, mouse models need to be validated by certain criteria. Historically, three criteria have been proposed to evaluate mouse models of mental disorders: (i) surface validity, which considers the similarity between behavioral characteristics of the mouse model and human symptoms; (ii) predictive validity, which assesses the efficacy of treatments for human mental disorders on the mouse model; and (iii) constructive validity, which investigates a shared mechanistic theory between the mouse model and the corresponding human disorder.[36-38]

Numerous behavioral tests has been developed to test the surface validity, assessing features such as locomotor activity, despair, anxiety-like behavior, working memory, social behavior, sensory processing, and cognitive function. Such tests are also essential for assessing predictive validity in mouse models. However, the cardinal psychiatric symptoms such as hallucinations, delusions, feelings of guilt, and suicidal ideation that place a huge burden on the private, domestic, and social lives of patients and their families are currently diagnosed based solely on the subjective reports of patients. These clinical manifestations present significant challenges for direct evaluation in mouse models. Therefore, evaluations of surface validity and predictive validity are feasible only in limited aspects of mental disorders. On the contrary, constructive validity provides a direct assessment of the potential pathophysiological mechanisms of mental disorders, regardless of symptoms. Thus, constructively valid mouse models based on high-risk variants are valuable tools for studying the mechanisms of mental disorders.

Therefore, mouse models that recapitulate the rare human pathogenic variants including 22q11.2 deletion have high constructive validity and allow a detailed evaluation of surface and predictive validity; the effects of the variant on behavior and underlying biological processes.

Assessing disease-relevant behavioral features

Genetically engineered mouse models mimicking variants identified by whole-genome analyses of patients with psychiatric disorders have been widely generated, with many undergoing behavioral phenotype analyses.[39] Among these, the prepulse inhibition test, a commonly used paradigm for assessing startled response, is considered an indicator of the SCZ-like phenotype. Additionally, visual discrimination tasks, which quantify sensory information processing ability by recognizing differences in features of images presented as visual stimuli, have been found to be impaired in SCZ-like models.[40]

Discussing interspecies differences in behavioral indices between humans and mice is always challenging; however, regarding 22q11.2DS (the strongest risk factor for SCZ), studies on patients and mouse models have been reported extensively. In 22q11.2DS patients, reductions in auditory prepulse inhibition, social interaction impairments, deficits in spatial working memory, and abnormalities in visual processing have been reported.[36,41-45] Similarly, in 22q11.2 DS mouse models, reductions in prepulse inhibition, changes in visual cognition, and social cognition impairments have been demonstrated.[33,41,46-48] Clinically effective antipsychotic drugs may have the potential to improve reductions in prepulse inhibition, warranting further investigation in future studies.[41]

Exploring neural circuit mechanisms underlying phenotypes

Structural and functional brain imaging and electroencephalography can effectively identify neural circuit abnormalities in patients with mental disorders.[42-44] However, they do not allow the manipulation of specific neuronal populations or circuits to determine their importance in behavioral phenotypes. Mouse models play a valuable role in this regard. Researchers can apply techniques in mouse models that are not feasible in human patients, such as optogenetics and in vivo 2-photon calcium imaging.[45,46] In particular, in vivo 2-photon calcium imaging is a powerful

tool for studying neurophysiological processes in neuronal populations. This method introduces genetically encoded fluorescent calcium indicators (GECIs) into the mouse brain. GECIs can detect neural activity by converting changes in calcium ion levels within activated neurons into changes in fluorescence intensity, thereby enabling the visualization and monitoring of neuronal population activity. Furthermore, along with optogenetics and other perturbation methods, in vivo 2-photon calcium imaging allows the investigation of causal relationships between neural circuits and behavioral phenotypes, thereby advancing our understanding of the neural basis of mental disorders.[47]

Recent studies have explored neural circuit mechanisms that explain disease-relevant sensory processing phenotypes. Disrupted thalamic inputs to the auditory cortex were identified as the causative neural circuit of reduced prepulse inhibition in 22q11.2DS model mice.[41] The study also showed that aberrant elevation of Drd2 expression in the thalamus due to the haploinsufficiency of *Dgcr8*, a gene in the 22q11.2 region, disrupts auditory thalamocortical projections. In evaluations of visual processing features, in vivo 2-photon calcium imaging revealed disorganized population activity of neurons in the primary visual cortex (V1) in a 22q11.2DS mouse model.[48]

In the aspect of disease development, a study in a 22q11.2DS mouse model showed that inhibition of Gsk3 during development could restore spatial working memory in navigational tasks and hippocampal-prefrontal connectivity and task-related neural activity deficits associated with SCZ.[49] Thus, this mouse might also be useful in the search for mechanisms of disease onset and development.

In recent years, there has been an increase in research attempting to elucidate the pathophysiology of psychiatric disorder model mice through calcium imaging studies. The *Setd1a* gene is an epigenetic regulatory factor in the histone H3K4 methylation pathway, and rare variants with loss of function have been reported to be strongly associated with SCZ onset.[50] Abnormal neuronal activity in the V1 neuronal population of *Setd1a* heterozygous deletion mice was identified.[51] This study revealed the low reliability of neuronal ensemble activity upon visual stimulation, indicating that visual information encoding is compromised in the mouse model.

As another research example, fragile X syndrome is known as one of the primary genetic causes of ASD, and *Fmr1*- knockout (*Fmr1*$^{-/-}$) mice have been extensively analyzed as models for fragile X syndrome.[52] A certain report focuses on the activity of V1 neurons during visual discrimination tasks in *Fmr1*$^{-/-}$ mice. This study shows that the performance of V1 neurons is decreased in *Fmr1*$^{-/-}$ mice. Additionally, in vivo, two-photon calcium imaging reveals impaired orientation selectivity of V1 neurons and reduced parvalbumin interneuron activity in response to visual stimuli.[53] By restoring the activity of parvalbumin interneurons, learning disabilities in *Fmr1*$^{-/-}$ mice can be alleviated.

Additionally, the processing of unisensory auditory and visual stimuli, the role of multisensory processing in the expression of psychiatric symptoms has also been investigated.[54] Studies on serotonin transporter Gly56Ala knock-in mice[55] (animal models of ASD) examined multisensory function by training mice to respond independently to auditory and visual stimuli before testing them under conditions involving visual, auditory, and audiovisual pairs.[56] It was revealed that the improvement in response accuracy under audiovisual conditions was suppressed. These studies shed light on the relationship between sensory information processing and symptoms observed in patients, providing valuable insights into the mechanistic basis of psychiatric disorders.

Searching for therapeutic candidates

Some studies have proposed promising directions for the identification of causative molecules in rare CNVs. An excellent example is a study that used a mouse model of 16p11.2 duplication syndrome.[57] This CNV, which spans a 600-kb region on human chromosome 16, is associated

with several neuropsychiatric disorders, including SCZ, ASD, and epilepsy. A mouse model that replicated this CNV (16p11.2dup/+ mice) demonstrated numerous behavioral and cognitive abnormalities, including altered locomotor activity, working memory, and repetitive and social behaviors and increased susceptibility to seizures. Neurons in these mice exhibit hypersynchronous activity and increased glutamate release. Proteomics and interactome analysis enabled the researchers to uncover disrupted synaptic and epilepsy-associated protein networks, identifying *Prrt2* as a central hub gene in this network.[57] The Prrt2 protein interacts with synaptic proteins such as t-SNARE and VAMP2.[58] Importantly, correcting the genetic function of *Prrt2* in the mouse model led to the mitigation of the neuronal phenotype for seizure susceptibility and psychiatric symptoms, including social deficits. This demonstrates the potential of gene-targeted therapy to address the causal genetic factors contributing to these neuropsychiatric conditions associated with rare CNVs.

Another example is the study of mouse models for Rett syndrome. The disease is caused by a deficiency in the X-linked transcription factor methyl-CpG-binding protein 2 (MECP2), a key regulator of gene expression in the CNS. Neonatal CSF delivery of the clinically optimized vector, scAAV9.P546.MECP2, could ameliorate the behavioral abnormality of *Mecp2* knockout mice.[59]

Linking insights from mouse models to human iPSCs

The utilization of mouse models mimicking variants implicated in the onset of psychiatric disorders identified in humans has enabled the biological characterization of these variants. While access to the human brain remains challenging, recent years have seen increasing interest in research utilizing iPSCs derived from patients with psychiatric disorders. Although methods for differentiating various types of neural cells, glial cells, and others from iPSCs in vitro have significantly advanced, three-dimensional constructions such as organoids are still in their developmental stages. Research on circuit pathology is expected to be promising in the future.

EXAMPLES OF MOUSE MODELS BASED ON RARE DISEASE-SUSCEPTIBLE VARIANTS

To date, we have produced several strains of mouse models based on disease-susceptible rare variants. Below, we report examples of our disease models derived from human subjects with rare psychiatric disease-susceptible variants. Our models are based on rare disease-susceptible variants; therefore, they are constructively valid models.[60-63] Further analysis of these models, including the neurophysiological properties underlying their phenotypes, will serve to elucidate the enigma of psychiatric diseases.

22q11.2 deletion

22q11.2DS is a neurogenetic disorder associated with high rates of SCZ and other mental disorders.[30] Several 22q11.2DS mouse model strains have been developed, including our model,[32-35] which recapitulate the most common 3.0-Mb deletion affecting over 30 protein-coding genes and the less common 1.5-Mb deletion and 1.4-Mb deletions.[64] Our Del(3.0 Mb)/+ mice showed reduced auditory prepulse inhibition and impaired early visual processing and social recognition, which are commonly observed in patients with SCZ.[65] While Del(1.5 Mb)/+ mice showed reduced auditory prepulse inhibition and impaired contextual- and cue-dependent fear memory, Del(1.4 Mb)/+ mice showed no abnormalities other than decreased locomotor activity in all behavioral tests performed.[66] Since the social recognition is apparently intact in both Del(1.4 Mb)/+ and Del(1.5 Mb)/+ mice, the impaired social recognition observed in Del(3.0 Mb)/+ mice was caused by the combined effect of deleted genes in 1.4-Mb and 1.5-Mb regions.[66] In the midbrain of

adult Del(3.0 Mb)/+ mice, PERK, the gene product of *Eif2AK3*, which is involved in endoplasmic reticulum stress signaling, was confirmed to decrease PERK levels compared with the wild-type. Similarly, a reduction in PERK protein levels was observed in dopaminergic neurons that differentiated from patient-derived iPSCs carrying the same variant.[67]

3q29 deletion

The 3q29 microdeletion is mostly de novo, and the incidence of the microdeletion is 1 in 30,000–40,000 births.[68] This microdeletion encompasses approximately 1.6 Mb in size, affects 22 genes, and is associated with several mental disorders.[69] In particular, it is one of the greatest risks for SCZ.[70] In addition to psychiatric conditions, the 3q29 microdeletion also causes speech delay and microcephaly.[68] Among the developed mouse models (including our own), there are those that replicate the human 3q29 microdeletion.[61,71,72] Mouse models of the 3q29 deletion (3q29 Df/+) have been created by three research groups so far, all of which have detected SCZ-like behavioral abnormalities. In our study, we observed features such as decreased prepulse inhibition, impaired social cognition, and reduced Parvalbumin-positive neurons in the cortex. These mice also exhibit dysfunction in the oxytocin system, suggesting its potential involvement in the pathogenesis of psychiatric disorders, including ASD.[71] Additionally, in circadian rhythm analyses, the 3q29 Df/+ mice showed hypersensitive characteristics during the transition from the light phase to the dark phase.[61] Molecular-level analyses are likely to become critical in the future.

RELN deletion

RELN encodes the large secreted protein reelin, which controls neuronal migration in the developing brain[73] and contributes to axonal guidance and synaptogenesis in the adult brain.[74] In the clinical context, patients with SCZ with exonic *RELN* deletions have exhibited a phenotype characterized by treatment resistance and low serum reelin levels.[75] In our *RELN* heterozygous deletion mouse model, we observed functional alterations in the dopaminergic and GABAergic systems, as well as abnormalities related to anxiety, social behavior, motor skills, and visual learning. This mouse model provides valuable insight into the effects of *RELN* haploinsufficiencies on neural function and behavior, enhancing our understanding of their relevance to mental disorders.[63,76]

ARHGAP10 variants

ARHGAP10, a susceptibility gene for SCZ identified through CNV analysis in Japanese patients with SCZ,[62] encodes a member of the RhoGAP (Rho GTPase-Activating Protein) superfamily of proteins involved in small GTPase signaling. This signaling pathway is associated with and contribute to neuronal development and function.[77-79] Among patients with SCZ with a deletion in the *ARHGAP10* region, one individual was identified with a missense variant (p.S490P) in the RhoGAP domain of *ARHGAP10*. This variant is relevant for the interaction between *ARHGAP10* and the active form of the protein RhoA.

Behavioral analysis of mice with the *ARHGAP10* variants mentioned above exhibited aberrant emotional behaviors and reduced spine density in the medial prefrontal cortex.[62] In addition, treatment with a Rho-kinase inhibitor ameliorated reduced spine density and altered emotional behaviors.[80] These findings suggest potential therapeutic effects of Rho-kinase inhibitors for SCZ patients with disease-susceptible *ARHGAP10* variants.

ASTN2 deletion

ASTN2 plays a critical role in regulating neuronal migration and synaptic strength by controlling the trafficking and degradation of surface proteins.[81] It is highly expressed in the adult brain.[82]

Analysis of CNVs has shown that deletion of *ASTN2* are associated with bipolar disorder, SCZ, and ASD.[17,83] A mouse model that recapitulates *ASTN2* deletion has shown several behavioral and neurobiological abnormalities, including increased abnormal social behaviors and impulsivity and decreased despair- and anxiety-like behaviors.[84] In addition, the model exhibits monoaminergic dysfunction and a reduced number of neurons and spine density in the hippocampus and prefrontal cortex.[84] These findings suggest that *ASTN2* plays a crucial role in regulating brain function, and its dysregulation may contribute to the development of mental disorders.

FUTURE PERSPECTIVES

As emphasized previously, the integration of findings from both patients and models across different etiologies is crucial to achieving a refined diagnosis and a comprehensive understanding of psychiatric diseases. In this vein, the identification of shared and distinct abnormalities have been attempted using multiple models.[85-87] Recent advancements in single-cell/nucleus RNA sequencing have emerged as valuable tools for investigating the transcriptome phenotype of various cell types, allowing for the detailed exploration of the effects of specific genes within large disease-susceptible CNVs.[88] The ongoing progress in this field, along with its application to mouse models and the integration of findings from iPSCs, brain imaging, and postmortem brain studies, should yield extensive insights into the pathogenesis of psychiatric diseases.

The common observable features shared between patients and mouse models are essential to unraveling the neural basis of psychiatric symptoms. Among these features, sensory information processing, including multisensory integration, is emerging as a promising research avenue. Research has focused on atypical sensory information processing in patients,[7,8,89] whose connections to psychotic symptoms have been hypothesized in predictive coding theory[10,11] and evaluated in patients.[9] Methods have been developed to freely design neuronal activities during behaviors and evaluate the causal relationship between neural activities and physiological. properties, thereby enabling detailed investigations of the neuronal circuit function underlying those phenotypes.[90-92] In addition, the rapid improvements in behavioral phenotype analysis[93,94] open new pathways to understanding the complex interplay between neural activities and behavioral phenotypes. The combination of these technologies with mouse models, including our own, will further enrich our understanding of the pathophysiology of mental disorders.

CONCLUSIONS

As we have explored in this study, advances in genetics and biology have allowed us to identify genetic variants associated with mental disorders and to assess the impact of these variants using various methods, including mouse models. We hope that these approaches, combined with ongoing technological advances, will contribute to the discovery of biomarkers, a deeper understanding of the pathophysiology of mental disorders, and the development of new therapeutic strategies. This pursuit holds great promise for improving the diagnosis and treatment of individuals with mental disorders.

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DISCLOSURE STATEMENT

The authors have no conflicts of interest to declare.

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