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Modeling common and rare genetic risk factors of neuropsychiatric disorders in human induced pluripotent stem cells

Abdurrahman W. Muhtaseb[a,b], **Jubao Duan**[a,c,*]

[a]Center for Psychiatric Genetics, NorthShore University HealthSystem, Evanston, IL 60201, United States of America

[b]Department of Human Genetics, The University of Chicago, Chicago, IL 60637, United States of America

[c]Department of Psychiatry and Behavioral Neuroscience, The University of Chicago, Chicago, IL 60637, United States of America

Abstract

Recent genome-wide association studies (GWAS) and whole-exome sequencing of neuropsychiatric disorders, especially schizophrenia, have identified a plethora of common and rare disease risk variants/genes. Translating the mounting human genetic discoveries into novel disease biology and more tailored clinical treatments is tied to our ability to causally connect genetic risk variants to molecular and cellular phenotypes. When combined with the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated (Cas) nuclease-mediated genome editing system, human induced pluripotent stem cell (hiPSC)-derived neural cultures (both 2D and 3D organoids) provide a promising tractable cellular model for bridging the gap between genetic findings and disease biology. In this review, we first conceptualize the advances in understanding the disease polygenicity and convergence from the past decade of iPSC modeling of different types of genetic risk factors of neuropsychiatric disorders. We then discuss the major cell types and cellular phenotypes that are most relevant to neuropsychiatric disorders in iPSC modeling. Finally, we critically review the limitations of iPSC modeling of neuropsychiatric disorders and outline the need for implementing and developing novel methods to scale up the number of iPSC lines and disease risk variants in a systematic manner. Sufficiently scaled-up iPSC modeling and a better functional interpretation of genetic risk variants, in combination with cutting-edge CRISPR/Cas9 gene editing and single-cell multi-omics methods, will enable the field to identify the specific and convergent molecular and cellular phenotypes in precision for neuropsychiatric disorders.

*Corresponding author at: Center for Psychiatric Genetics, NorthShore University HealthSystem, Evanston, IL 60201, United States of America. jduan@uchicago.edu (J. Duan).

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1. Introduction

The last decade of psychiatric research has witnessed the success of genome-wide association studies (GWAS). Through unbiased genome-wide interrogation of millions of genetic markers, i.e., single nucleotide polymorphisms (SNPs), in large population case/control samples, GWAS of schizophrenia (SZ) and other neuropsychiatric disorders have identified hundreds of risk loci with common genetic risk variants (Psychiatric Genomics Consortium-Schizophrenia, 2011; Psychiatric Genomics Consortium-Schizophrenia, 2014; Mullins et al., 2021; PGC3 et al., 2020; Purcell et al., 2009; Ripke and Concortium, 2013; Shi et al., 2009; Stefansson et al., 2009). Of these, SZ GWAS has the most successes: the recent Psychiatric Genomics Consortium (PGC) (PGC2) reported 145 genome-wide significant SZ risk loci (Psychiatric Genomics Consortium-Schizophrenia, 2014; Pardinas et al., 2018), which were further expanded by the upcoming PGC wave 3 (~270 SZ risk loci) (The Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020). The common disease risk variants implicated by these GWAS often have small population effect sizes (odds ratios, OR < 1.2) (Bassett et al., 2010; Levinson et al., 2011; Marshall et al., 2017; Szatkiewicz et al., 2014), hindering the mechanistic understanding of disease pathophysiology.

These genome-wide studies in large samples also revealed another side of the risk spectrum for neuropsychiatric disorders: rare copy number variants (CNVs, i.e., genomic segments that are duplicated or deleted) of higher penetrance. SZ has the largest number of reproducibly associated CNVs, which include deletions at 1q21.1, 2p16.3 (*NRXN1*), 3q29, 15q13.3, distal 16p11.2, 22q11.2, and duplications at 7q11.23 and proximal 16p11.2 (Bassett et al., 2010; Levinson et al., 2011; Marshall et al., 2017; Szatkiewicz et al., 2014). These rare and large (usually >100 kb) CNVs often show much larger effect sizes (OR of 2–70) than common SNPs (OR < 1.2) (Bassett et al., 2010; Levinson et al., 2011; Marshall et al., 2017; Szatkiewicz et al., 2014). Besides these rare CNVs, recent large-scale whole-exome sequencing (WES) studies have also unraveled rare protein-coding variants that are associated with SZ with relatively large effect sizes (Singh et al., 2017). By analyzing exome variants in 24,000 SZ patients and 97,000 controls, the SZ Exome Sequencing Meta-Analysis (SCHEMA) Consortium reported ~10 genes with ultra-rare loss-of-function (LoF) mutations (or protein-truncating variants) that collectively reached genome-wide significant association with SZ (Singh et al., 2020). Together with common disease risk variants identified from GWAS, these genetic findings have provided unprecedented opportunities for the neuropsychiatric field to better understand disease biology.

Despite the tremendous progress made in identifying neuropsychiatric risk variants, effective treatments of these disorders remain scarce and largely rely on old drugs. For instance, most antipsychotic drugs for treating positive symptoms of SZ target dopamine D2 receptors

(DRD2), a discovery that was made almost half a century ago (Creese et al., 1976; Howes et al., 2012; Seeman and Lee, 1975; Snyder, 1976). Furthermore, their use has been impeded by side effects such as extrapyramidal symptoms and tardive dyskinesia (Nasrallah, 2008). Although atypical antipsychotic drugs such as clozapine and risperidone can improve negative symptoms, and cognitive function with fewer extrapyramidal symptoms by targeting not only DRD2 but also non-dopamine targets such as serotonin and glutamine, such non-specificity of targets may contribute to a number of side effects of concern, e.g., weight gain, glucose dysregulation and dyslipidemia. Thus, translating these genetic findings of neuropsychiatry into novel disease biology and potentially more tailored clinical interventions is highly needed, which requires not only our conceptual understanding of the complexities of polygenic neuropsychiatric disorders but also a comprehensive approach that integrates knowledge from different experimental models.

Human postmortem brain tissues and animal models (Carlson et al., 2011; Dong et al., 2013; Jeong et al., 2006) have provided invaluable insights into plausible disease pathophysiology, but each model has its pros and cons. The postmortem brain is not living tissue and mostly does not capture changes at early neuronal developmental stages (Brennand et al., 2015). Furthermore, postmortem brain study is well-known for confounding factors related to tissue variability and some uncontrollable environmental factors (Lipska et al., 2006), and the postmortem brain is not amenable to genetic modification. Although rodent models can be genetically modified for studying psychiatric disorders, they often do not faithfully recapitulate human pathophysiology and behaviors. Moreover, because regulatory variants are often species-specific (Shen et al., 2012), animal models may not elicit the expected functional impact of human genetic variations (Johnson et al., 2009). Peripheral blood cells and B-cell transformed lymphoblastoid cell lines (LCLs) from psychiatric patients and controls of relatively large numbers have also been used as ex vivo models to reveal disease genetic effects on gene expressions (Arloth et al., 2015; Duan et al., 2018; Kos et al., 2018; Mostafavi et al., 2014). For instance, with LCLs of over 1000 SZ cases and controls, we found that the disease-associated differentially expressed genes upon cellular stimulation by dopamine (DA) were enriched for genes related to immune processes and apoptosis as well as mitochondrial oxidative phosphorylation, and interestingly, were overrepresented by those near genome-wide significant SZ loci and within SZ-associated CNVs (Duan et al., 2018; Kos et al., 2018). Although blood cells and LCLs may be useful in providing mechanistic insight for disease risk factors related to the long-standing immune hypothesis of the neuropsychiatric disorder (Heath and Krupp, 1967; Pouget, 2018; van Mierlo et al., 2020), such a cellular model has its obvious limitations, i.e., further-removed from the brain that is presumably the most relevant tissue for neuropsychiatric disorders.

Compared with postmortem brains or animal models, stem cell-based cellular models provide a promising alternative for studying common and rare genetic risk factors of neuropsychiatric disorders (Panchision, 2016; Wen et al., 2016). Benefiting from the revolutionary induced pluripotent stem cell (iPSC) technology discovered by Dr. Yamanaka (Takahashi et al., 2007; Takahashi and Yamanaka, 2006), somatic cells such as fibroblasts or blood cells from patients or healthy controls can be reprogramed into pluripotent stem cells (i.e., human iPSCs) simply by exogenously expressing some transcription factors (i.e., Yamanaka factors: Oct3/4, Sox2, Klf4, c-Myc) (Takahashi et al., 2007; Takahashi and

Yamanaka, 2006). iPSCs can then be re-differentiated into different brain cell types that are relevant to neuropsychiatric disorders. iPSC model enables studying disease-relevant molecular and cellular phenotypic changes in a temporal and cell type-specific manner. More importantly, iPSC models are amenable to genetic modification or epigenomic perturbation, which is important for studying the functional impacts of disease risk variants. When combined with the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated (Cas) nuclease-mediated genome editing system (Cong et al., 2013; Fu et al., 2013; Mali et al., 2013; Sander and Joung, 2014; Shalem et al., 2014; Wang et al., 2013), iPSC-derived neurons represent a powerful cellular model for understanding disease biology underlying neuropsychiatric genetic findings. In light of previous reviews about using iPSC models for studying psychiatric disorders over the years (Das et al., 2020; De Los Angeles et al., 2021; Dolmetsch and Geschwind, 2011; Duan, 2015; Duan et al., 2019; Durak and Tsai, 2014; Fernando et al., 2020; Hoffmann et al., 2019; Jacobs, 2015; Michael Deans and Brennand, 2021; Miller and Kelsoe, 2017; Quadrato et al., 2016; Rajarajan et al., 2020; Soliman et al., 2017; Temme et al., 2016; Wen et al., 2016; Wright et al., 2014; Young-Pearse and Morrow, 2016), here we will focus on conceptualizing the key advances in the field (Fig. 1, Table 1 and Table S1), the validity of the model, interpretation of the results, limitations and new research opportunities.

2. What to model: rare vs. common disease risk variants

Translating the mounting human genetic discoveries into novel disease biology and more tailored clinical treatments is tied to our ability to causally connect genetic risk variants to molecular and cellular phenotypes. iPSC model has been used for studying the functional impacts of both rare and common disease risk variants. Depending on the effect size of a modeled variant, either patient-specific iPSC lines or CRISPR-engineered isogenic iPSC lines have been employed. However, because of the polygenic nature of neuropsychiatric disorders, regardless of the variant penetrance or the experimental design, the resulting molecular and cellular phenotypes may be confounded by the individual donor's genetic background and need to be interpreted cautiously.

2.1. Rare CNVs

There are overwhelmingly more studies of iPSC modeling of rare disease-associated CNVs, of which autism and SZ are the two most commonly modeled disorders. The large effect sizes of these CNVs make them "low-hanging fruits" among other genetic findings, an ideal model for understanding disease biology and interpreting the disease relevance of cellular phenotypes. Of the CNVs with established reproducible associations with SZ and/or autism at 1q21.1, 2p16.3 (*NRXN1*), 3q29, 7q11.23, 15q13.3, 16p11.2, and 22q11.2 (Bassett et al., 2010; Levinson et al., 2011; Marshall et al., 2017; Szatkiewicz et al., 2014), all except for the SZ-associated 3q29 deletion (Sefik et al., 2020) have at least one iPSC modeling study that reported a cellular phenotype (Adamo et al., 2015; Avazzadeh et al., 2021; Chailangkarn et al., 2016; Chapman et al., 2021; Crockett et al., 2021; Flaherty et al., 2019; Gillentine et al., 2017; Khan et al., 2020; Khattak et al., 2015; Lalli et al., 2016; Li et al., 2021a; Li et al., 2021b; Roth et al., 2020; Sundberg et al., 2021; Toyoshima et al., 2016; Zanella et al., 2019; Zhang et al., 2021b) (Table 1). Because of their large

effect sizes, these studies exclusively use patient-specific iPSC lines, i.e., directly derived from patients who carry the CNV, except for one that used CRISPR-Cas9 engineered 16p11.2 duplication (16pdup) and 16p11.2 deletion (16pdel) (Sundberg et al., 2021). The patient-specific CNV carriers are then compared with matched population control lines to determine any meaningful molecular (i.e., often transcriptomic profile) and/or cellular phenotypic characteristics associated with a CNV. Because these CNVs tend to be extremely rare in the population, individual studies often have a very small sample size, ranging from 1 to 15 patient lines. Not surprisingly, the largest study (n = 15 cases) was with 22q11.2 deletion (Khan et al., 2020), the most prevalent CNV with the strongest association with SZ.

Likely due to the small and variable number of CNV carriers in each study, despite the high penetrance of these studied CNVs, iPSC modeling studies frequently yield discordant phenotypes. Even for the same CNV, different studies often test different hypotheses and report discordant molecular and cellular phenotypes. For instance, the largest study of 22q11.2 deletion (Khan et al., 2020) analyzed transcriptomic profiles at different developmental stages of patient-specific iPSC-derived cortical spheroids and identified a deficit gene pathway related to calcium channel activity. Interestingly, although neurons dissociated from the cortical spheroids of 22q11.2 deletion delayed spontaneous hyperactivity, their calcium transmission activity was found significantly impaired upon neuronal depolarization, which can later be reversed by antipsychotic drugs targeting *DRD2* (Khan et al., 2020). However, two other studies of patient-specific 22q11.2 deletions reported dysfunction of mitochondria biogenesis and blood-brain barrier (BBB), respectively (Crockett et al., 2021; Li et al., 2021b). For another commonly modeled CNV region, SZ-associated 16pdup and autism-associated 16pdel, one study using patient-specific CNV carriers revealed increased soma size and dendrite length in 16pdel neurons and reduced neuronal size and dendrite length in 16pdup neurons, and interestingly, both 16pdel and 16pdup neurons (excitatory) displayed reduced synaptic density (Deshpande et al., 2017). Although seemingly consistent neuronal hyperactivity was reported for CRISPR-engineered 16pdel, it was only observed in iPSC-derived dopaminergic neurons and no obvious phenotype was observed for 16pdup (Sundberg et al., 2021). Moreover, of the two other studies of patient-specific 16pdel, one reported that the overexpression of CD47 (a “don’t eat me” signal) in both neural progenitor cells (NPCs) and oligodendrocyte progenitor cells (OPCs) of 16pdel carriers may contribute to the reduced phagocytosis and brain overgrowth in autism-associated macrocephaly (Li et al., 2021a), while the other study found substantial transcriptional alterations associated with early neural development without any reported cellular phenotypic changes in 16del carriers (Roth et al., 2020).

Alternatively, such phenotypic discrepancies may be attributed to the fact that these large CNVs span multiple genes. However, even for 2pl6.3 deletion that only involves a single gene, *NRXN1*, there are still inconsistencies between different studies. A multi-center study of *NRXIV1*-deletion lines reported a large decrease of spontaneous synaptic events, evoked synaptic responses, and synaptic paired-pulse depression in excitatory neurons, regardless of genetic backgrounds (Pak et al., 2021). While the reduced neuronal activity in *NRXIV1*-deletion lines was also observed in another study (Flaherty et al., 2019), a most recent study seemed to show larger sodium currents, higher AP amplitude, and accelerated depolarization time, i.e., increased excitability, in cortical neurons carrying *NRXN1* deletion (Avazzadeh

et al., 2021). Therefore, the discrepancies across iPSC modeling of CNVs were likely due to the intrinsic clinical heterogeneity associated with each CNV and the effects of individual genetic backgrounds. Future iPSC modeling of CNVs with an increased number of patient-specific iPSC lines in combination with CRISPR-engineering of CNVs may help improve the consistency and identify more convergent disease-specific phenotypes.

Because these rare CNVs are usually long (>100 kb) and span multiple genes, it has been a challenge to identify which gene(s) within a CNV region are likely the driver(s) for disease-relevant phenotypes. The challenge is amplified by the possible effects of a CNV on local or distal chromatin architecture and, consequently, the expression of genes outside the CNV region (Franke et al., 2016; Redin et al., 2017). iPSC model in combination with CRISPR/Cas9 gene editing or CRISPRi/CRISPRoff (Kampmann, 2020; Nunez et al., 2021) to knockdown (KD) individual gene expression within a CNV would be an effective approach to solve the problem. The only iPSC modeling study that made such a systematic effort was for 15q13.3 microdeletion by analyzing the transcriptomic similarity of individual gene KD with the entire CNV in day-6 (post neural induction) neurons, which however did not point to any specific gene (Zhang et al., 2021b). The imprecision of mapping the drive gene(s) in this study (Zhang et al., 2021b) may be improved by using more mature neurons (e.g., 4 weeks rather than day-6 neurons). Towards this end, in an independent study, combining with targeted resequencing of CNV genes in an SZ case/control cohort and iPSC modeling of the patient-specific loss-of-function (LoF) mutation of *OTUD7A* (OTU Deubiquitinase 7A), we found that *OUTD7A* LoF resulted in reduced dendrite complexities, synaptic protein puncta densities in spines, and impaired electrophysiology (Kozlova et al., 2022), which recapitulates the cellular phenotypes of the CNV modeling in animals (Yin et al., 2018), supporting *OUTD7A* as a plausible driver gene for 15q13.3 microdeletion.

2.2. Rare protein-coding variants

Most iPSC modeling of rare protein-coding variants, including missense or protein-truncating mutations, is for monogenic-like autism spectrum disorders. Both patient-specific iPSC lines carrying the modeled mutations or isogenic lines with CRISPR-engineered mutations were used. The modeled mutations tend to be extremely rare or de novo that have already been extensively studied in rodents or other model organisms, and iPSC modeling mostly recapitulates the known cellular phenotypes. Overall, the resulted cellular phenotypes in human neurons for these mutations can be classified into two categories: (1) hypofunction such as reduced calcium signaling and activity-dependent dendrite retraction for a missense mutation in the L-type calcium channel Ca(v)1.2 (Krey et al., 2013; Panagiotakos et al., 2019; Pasca et al., 2011), reduced action potentials and peak inward currents for mutations in methyl-CpG-binding protein 2 (*MECP2*) (Farra et al., 2012); fewer synapses and defects in excitatory synaptic neurotransmission for mutations in postsynaptic *SHANK3* (Kathuria et al., 2018; Shcheglovitov et al., 2013) and aberrant dendritic spines for *CDKL5* mutations (Ricciardi et al., 2012); (2) hyperfunction such as increased neural progenitor proliferation and organoid overgrowth for protein-truncating LoF mutation in *CNTNAP2* (de Jong et al., 2021), accelerated dendritic morphogenesis and enhanced excitatory synaptic strength for LoF variants in *SYNGAP1* (Llamosas et al., 2020), and increased dendrite length,

complexity, synapse number, and frequency of spontaneous excitatory postsynaptic currents and hyper-connectivity for *SHANK2* mutations (Zaslavsky et al., 2019).

Compared to autism risk variants/genes, very few rare risk variants of other neuropsychiatric variants have been modeled in iPSC-derived human neurons. This reflects the different genetic risk architecture of autism spectrum disorders from other psychiatric disorders: autism is more monogenic and has much more established disease-associated protein-coding variants. The most studied rare risk variant is a frame-shift mutation of disrupted in schizophrenia 1 (*DISC1*) that is co-segregated with major psychiatric disorders in a single family (Millar et al., 2000). Despite the lack of support from the SZ GWAS (PGC2, 2014; PGC3 et al., 2020) or other large-scale exome sequencing projects such as SCHEMA (Singh et al., 2020), the isogenic iPSC lines carrying the *DISC1* mutation showed a deficit of synaptic vesicle release and dysregulated expression of genes related to synapses and psychiatric disorders in iPSC-derived forebrain neurons and brain organoids, when the iPSC-derived cells are cultured in a three-dimensional fashion instead of monolayers on a dish, which was also consistent with the results from humanized *DISC1* mutant mouse model (Wen et al., 2014; Ye et al., 2017). Similarly lacking strong genetic association evidence, two rare missense mutations Chondroitin Sulfate Proteoglycan 4 (*CSPG4*) that showed familial segregation with SZ (de Vrij et al., 2019) and a missense mutation, E492K, in *NTRK1* that showed familial segregation with bipolar disorder (BP) (Nakajima et al., 2020) were also modeled in iPSC-derived neurons. Given that large exome sequencing projects such as SCHEMA (Singh et al., 2020) start to reproducibly identify rare protein-coding variants associated with SZ and other neuropsychiatric disorders, we anticipate more iPSC modeling of rare protein-coding variants, which will help improve our mechanistic understanding of the contribution of rare protein-coding variants to neuropsychiatric disorders.

2.3. Common variants

Because common GWAS risk variants explain much more disease liability than rare risk variants of high penetrance, it is imperative to tie putative causal GWAS risk SNPs with functionality to understand disease causal mechanisms. iPSC model in combination with CRISPR-based precise SNP allele editing provides a powerful approach to bridge the GWAS findings to novel disease biology. However, modeling common GWAS risk variants is challenging for several reasons:

(1) for most GWAS risk loci, each has many common SNPs equally associated with disease and often spans multiple genes due to linkage disequilibrium (LD), it is difficult to determine which are the likely functional and causal variant/gene to model; (2) most common risk variants are in the noncoding part of the genome and do not change protein sequence, rather regulating gene expression; (3) more importantly, common risk variants have small population effect sizes, which may make it challenging to detect any biological function.

Because of these challenges, modeling common GWAS risk variants often requires prioritization of putatively functional/causal SNPs by integrative computational fine mapping of causal SNP and/or functional genomics interrogation of their putative

functionality, e.g., by brain expression quantitative trait locus (eQTL) analysis or chromatin accessibility mapping (Dobrindt et al., 2020; Forrest et al., 2017; Schrode et al., 2019; Zhang et al., 2021a; Zhang et al., 2020). As regulatory variants are often cell-type and developmental stage-specific (Civelek and Lusis, 2014; Nica et al., 2013; Paul et al., 2014), iPSC modeling of common risk variants may need to assay for temporal changes of transcriptional and cellular effects of common variants at different neural differentiation stages. With regard to the feasibility to detect meaningful biological function for common risk variants of small effect sizes, it is arguably proven that simple cellular models like iPSC-derived neurons may reduce the system's "buffering" to genetic or environmental perturbations compared to the whole organism (Merkle and Eggan, 2013), and common GWAS risk variants can still elicit moderate or even strong effects on molecular/cellular phenotypes (Bauer et al., 2013; Corradin et al., 2014; Kulzer et al., 2014; Miller et al., 2014; Musunuru et al., 2010; Spieler et al., 2014). Furthermore, even assuming a homozygous common GWAS risk variant causes a 20–30% difference of gene expression, the magnitude of the functional impact is not too different from a theoretically 50% reduction of gene expression or protein function resulting from a heterozygous rare LoF mutation of high penetrance. Moreover, it is very likely a subtle expression change may result in an amplified downstream cellular phenotype alteration, for instance, ~ 15% KD of expression of an Alzheimer's disease GWAS risk gene, *PICALM*, in astrocytes leads to >50% reduced endocytosis of neuron-derived lipids (Moulton et al., 2021).

We and others have recently successfully studied functional impacts of common GWAS risk variants of SZ in CRISPR-engineered isogenic iPSC-derived neurons. As a proof of concept, we prioritized putatively functional SZ GWAS risk variants through co-localization with open chromatin peaks, and for a leading SZ risk locus spanning *M1R137*, we showed that the risk allele of common GWAS risk SNP rs1198588 was associated with altered *M1R137* promoter chromatin openness, reduced *MIR137* expression, and accelerated neuronal maturation (Forrest et al., 2017). More recently, we systematically mapped putatively functional SZ GWAS risk variants that showed differential allelic chromatin accessibility (i.e., allele-specific open chromatin or ASoC) and affect gene expression in iPSC-derived NPCs, glutamatergic neurons, GABAergic neurons, and dopaminergic neurons (Zhang et al., 2020). For the strongest ASoC SNP (rs2027349) associated with SZ at the vacuolar protein sorting 45 homolog (*VPS45*) locus, we found rs2027349 editing altered the expression of *VPS45*, lncRNA *AC244033.2,* and a distal gene, *C1orf54,* in human neurons. Neurons carrying the risk allele exhibited increased dendritic complexity, synaptic puncta density, and hyperactivity, which were reversed by knocking-down distinct cis-regulated genes (*VPS45*, *AC244033.2,* or *C1orf54*), suggesting a phenotypic contribution from all three genes (Zhang et al., 2021a). Similar to our demonstrated compound non-additive effects from all three genes at the same GWAS locus (Zhang et al., 2021a), another earlier study elegantly showed that common GWAS risk variants/genes, prioritized by brain eQTL mapping, from several different risk loci (*FURIN*, *SNAP91, TSNARE1,* and *CLCN3*), may synergistically affect the expression of genes involved in SZ pathogenesis in iPSC-derived neurons (Schrode et al., 2019). These studies suggest that noncoding GWAS risk variants impact the neurodevelopmental aspect of SZ and show a detectable biological function in iPSC-derived neurons.

Despite the initial success of iPSC modeling of common GWAS risk variants of neuropsychiatric disorders, functional interpretation of the cellular and molecular effects of individual variants in a small sample can be challenging. This is largely due to the small effect sizes of common risk variants and some confounding factors such as variable genetic backgrounds and intrinsic iPSC clonal variation. As a result of purifying selection against deleterious mutations in the population (Cvijovic et al., 2018; Gibson, 2012), the small effect sizes of common risk variants are expected to yield small magnitude of biological effects. In addition, buffering effects from genes in the same biological pathway and/or other allele(s) in the same haplotype background as the risk allele (Gibson, 2012; Hartman et al., 2001) may further complicate the detection and interpretation of any biological effects of common risk variant/gene in iPSC modeling. In this regard, it is noteworthy that, Peng et al. recently showed that the GWAS eQTL variants associated with SZ can have an effect on the expression of some target genes that is inversely correlated with SZ risk (Peng et al., 2021). A systematic and unbiased massive parallel approach will be needed to overcome these limitations to better model common GWAS risk variants (Townsley et al., 2020). Moreover, given that common GWAS risk genes may often act together as part of gene networks, multiplex SNP/gene editing to perturb different genes at the network level will be needed for iPSC modeling of common GWAS risk variants.

2.4. Polygenic risk

Both GWAS of neuropsychiatric disorders (Psychiatric Genomics Consortium-Schizophrenia, 2011; Psychiatric Genomics Consortium-Schizophrenia, 2014; Mullins et al., 2021; PGC3 et al., 2020; Purcell et al., 2009; Ripke and Concortium, 2013; Shi et al., 2009; Stefansson et al., 2009) and large-scale postmortem brain transcriptome studies (e.g., by PsychENCODE) (Fromer et al., 2016; Gandal et al., 2018; Wang et al., 2018) revealed the polygenic nature of neuropsychiatric disorders (Schizophrenia Working Group of the Psychiatric Genomics, 2014; Sullivan et al., 2018). Although modeling individual common GWAS risk variants or rare risk variants can help understand disease mechanisms at individual loci, it is also important to determine the convergent functional effects of polygenic risk on disease-relevant cellular and molecular phenotypes. One of the first iPSC modeling studies of the polygenic risk of neuropsychiatric disorders was with SZ using 4–5 cases compared to matched controls (Brennand et al., 2011). Despite a very small sample, biologically meaningful transcriptomic differences were identified between the SZ case and control iPSC-derived neurons (Brennand et al., 2011). Due to the technical challenge of scaling up the iPSC work, the reported largest case/control sample size in studies aiming to model polygenic effects remains too small, with cortical interneurons of 14 SZ cases and 14 controls (Shao et al., 2019). Likely because of the small sample size, only dysregulated expression of protocadherin genes and protocadherin relevant neuronal phenotypes were identified (Shao et al., 2019).

With small samples that do not reflect the polygenic risk spectrum of neuropsychiatric disorder, reducing the clinical heterogeneity of hiPSC lines by selecting subjects with common clinical manifestations or with rare genetic variants would be critical for drawing meaningful but limited insights (Brennand et al., 2014). Alternatively, because individual polygenic risk score (PRS) often correlates with the severity of disease symptoms or

resilience (Hess et al., 2019; Zhang et al., 2019), selecting iPSC lines from donors with extreme PRS may help improve the study power of iPSC modeling of neuropsychiatric disorders. For instance, with iPSC-derived neural progenitors and cortical neurons from 13 SZ individuals with high PRS for SZ, along with 15 neurotypical individuals with low PRS, Page et al. identified neural electrophysiological measures associated with a diagnosis that implicated altered Na+ channel function and GABAergic neurotransmission (Page et al., 2021). However, due to complex yet unclear interactions between rare risk variants and/or non-genetic risk factors (e.g., stress) with individual polygenic risk backgrounds, the results from such study design of comparing patient group of high PRS to control group of low PRS may not reflect the difference between patients of low PRS and healthy controls of high PRS. Regardless, the mechanistic insight on the polygenic risk effects from studies with small sample sizes remains limited. Investigating a sufficient number of samples from each PRS group, affected or healthy, on cellular and genomic/transcriptomic levels, may give us leads to what may be the reliable and valid cellular phenotypes relevant to neuropsychiatric disorders.

With a limited sample size at this time, the iPSC modeling of polygenic risk may benefit from a focused study of the effect of PRS on phenotypic expressivity of rare and highly penetrant risk variants. Patients who carry rare disease risk variants often have an excess burden of common GWAS risk alleles (Tansey et al., 2016). The field has started to understand the interplay between PRS and highly penetrant rare risk variants such as the well-known 22q11 deletion (Cleynen et al., 2020). Some top-ranking genes identified by SCHEMA to have rare but highly penetrant SZ-associated protein-truncating or LoF mutations (Singh et al., 2020) may also be such candidates for exploring PRS effects. For example, for the strongest SZ candidate gene in the SCHEMA study, *SETD1A,* its LoF mutations are highly penetrant (OR = 20; similar to that of SZ-associated 22q11 deletion) (Singh et al., 2020). However, LoF-mutation-carriers do not always develop SZ rather show other neurodevelopmental phenotypes. Such incomplete penetrance or phenotypic heterogeneity may be explained by individual genetic risk backgrounds: the variable phenotypic expressivity may be modulated by common SZ risk loci, either through additive or synergistic effects, resulting in disease resilience (by low PRS) or vulnerability (by high PRS). iPSC lines with high or low extreme PRS of neuropsychiatric disorders would be very useful for modeling such polygenic risk effects.

In this regard, it is noteworthy that we have recently built a small cohort of iPSC lines with extreme SZ PRS (Dobrindt et al., 2020). These iPSC lines were selected from a few thousand donor lines at the California Institute of Regenerative Medicine (CIRM), representing the extreme PRS compared to the rest. These lines have been characterized for their pluripotency, cell growth, transfection efficiency, neuronal differentiation, and CRISPR-editing efficiencies (Dobrindt et al., 2020). Although a small sample, a cohort of well-characterized iPSC lines is expected to be useful for generating isogenic lines for the functional study of SZ risk variants in the context of high/low PRS backgrounds. However, given the nature of phenotypic heterogeneity and the small population effect size of common variants, even with an isogenic approach the selection of PRS backgrounds in CRISPR-editing needs to be carefully considered. Because of additive effect from risk variants, although unproven, introducing a common risk variant on top of a healthy subject

with high SZ PRS may be more likely to yield disease relevant cellular phenotypes, which otherwise may be confounded by effects from non-genetic or rare genetic risk factors on a patient genetic background. Conversely, for modeling rare risk variants of high penetrance, a CRISPR-editing experiment may benefit from "correcting" a risk allele on a patient genetic background in addition to independently introducing a risk allele on a healthy genetic background of high SZ PRS. Nonetheless, CRISPR-editing on different type of genetic backgrounds is imperative for obtaining more reliable and interpretable disease-relevant cellular phenotypes.

3. Which model: 2D vs. 3D neuronal culture systems

Both 2D and 3D neuronal cultures (i.e., organoids) derived from human iPSCs of donors with different genetic backgrounds, or from CRISPR-engineered isogenic lines, are promising tractable cellular models for neuropsychiatric disorders (Duan et al., 2019; Kampmann, 2020; Townsley et al., 2020). Because these neural cultures only recapitulate early neurodevelopment processes, they are most suitable for modeling psychiatric disorders with neurodevelopmental aspects, i.e., autism and SZ. While the 2D culture has been widely used for modeling both common and rare risk variants, 3D cortical or brain organoids have been mainly used to model rare risk variants of large effect sizes.

3.1. 2D culture: monolayer neurons or co-culture system

All major brain cell types (NPCs, glutamatergic, GABAergic, dopaminergic, and cholinergic neurons, oligodendrocyte, astrocyte, and microglia) can now be efficiently differentiated from iPSC (Barretto et al., 2020; Butler Iii et al., 2020; Dobrindt et al., 2020; Douvaras and Fossati, 2015; Giacomelli et al., 2022; McQuade et al., 2018; Yang et al., 2017; Zhang et al., 2020; Zhang et al., 2013). Because of the relatively high efficiency of differentiation and high purity of each iPSC-derived cell type, the 2D culture system has been widely used for studying neuropsychiatric, neurodevelopmental, and neurodegenerative disorders. For instance, forced exogenous expression of NGN2 gives rise to near 100% excitatory neurons (NGN2-iNs) in about 4 weeks (Vierbuchen et al., 2010; Zhang et al., 2013), which makes NGN2-iNs the most commonly used cellular model for studying both common and rare risk factors of neuropsychiatric disorders (Table 1). The relatively homogenous population of differentiated cells also makes it straightforward for transcriptomic analysis by RNA-seq, morphological and electrophysiological analyses. Compared to the postmortem brain, which is well-known to be confounded by tissue variability and environmental factors (Lipska et al., 2006), hiPSC differentiation into neurons can be better controlled, thus making the data more reproducible.

The wide use of 2D culture systems often comes with methodological variations, which may yield different cellular phenotypes that need careful interpretation. For instance, Compared to NGN2-INs directly derived from iPSC, excitatory neurons differentiated from iPSC-derived NPCs represent a slower process but better recapitulates normal neurodevelopmental processes (Wang et al., 2019; Wen et al., 2014). Moreover, on some occasions of modeling neuropsychiatric risk variants, the neural electrophysiological phenotype may be observed in NPC-differentiated excitatory neurons but not in NGN2-INs (personal communication

with Dr. Zhiping Pang). By comparing the inhibitory neurons directly derived from iPSC (Yang et al., 2017) and those derived from NPCs (Barretto et al., 2020), we also noted their different electrophysiological characteristics (Dobrindt et al., 2020). Such discrepancies may be due to the variable maturation stages and/or regional identity of the seemingly pure iPSC neurons, a reasoning that was supported by some recent single-cell RNA-seq analysis of the seemingly pure cell populations of NGN2-INs (based on immunofluorescence staining) contain cells of different maturity and even not the expected cortical identify (Wang et al., 2021; Zhang et al., 2021a).

Although 2D culture has the advantage of being relatively homogenous, it is not reminiscent of in vivo neural environment. An improved 2D culture system is the co-culture of excitatory and inhibitory neurons, or at a defined ratio, i.e. 80:20%, that is similar to the neuronal composition of the forebrain (Sahara et al., 2012). Human neurons will then be co-cultured with monolayer glial cells to facilitate maturation and synaptogenesis (Pang et al., 2011; Ullian et al., 2001; Vierbuchen et al., 2010). The cellular phenotypes can be assayed by differentially labeling excitatory and inhibitory neurons in the co-culture and the transcriptomic changes can be interrogated by scRAN-seq. With such a co-culture design, Wang et al. elegantly demonstrated that human knock-in neurons carrying the autism risk variant (R451C) in the NLGN3 gene decreased NLGN3 protein level and enhanced the strength of excitatory synapses without affecting inhibitory synapses (Wang et al., 2021).

3.2. 3D culture: spheroids or organoids

Brain organoids have anatomical structures reminiscent of the developing human brain thus presenting a promising approach for studying early neurodevelopment and for modeling risk factors for neurodevelopmental disorders (Pasca et al., 2015; Paşca, 2019; Quadrato et al., 2016; Rigamonti et al., 2016). Among different types of methods for generating brain organoids or spheroids, cortical spheroids as part of the assembloids have been more commonly used due to their relatively better reproducibility and simplicity (Paşca, 2019). However, for most methods, because of the cellular stress and cell death posed by the lengthy process of organoid development (months), cortical layer expansion and the size of cortical plate of the differentiated brain organoids are usually not reminiscent of the human cortical structure. This limitation can be mitigated by a recently developed method, a sliced neocortical organoid (SNO) system (Qian et al., 2020). This method is based on a previously established protocol using bioreactors (Qian et al., 2018; Qian et al., 2016) in generating cortical organoids, now combined with brain organoid slicing and culturing in vitro, resulting in sustained neurogenesis and radial migration of newborn neurons (Qian et al., 2020). Consequently, SNO forms an expanded cortical plate that establishes distinct upper and deep cortical layers, with diverse subtypes of neurons and astrocytes. The SNO largely resembles the third-trimester embryonic human neocortex (Qian et al., 2020), which will be ideal for studying neurodevelopment and for quantifying the morphological and cellular compositional changes associated with neuropsychiatric risk factors.

Besides the anatomical or morphological resemblance of brain organoids to developing human brains, at a molecular level, what is the validity of the 3D organoid model or how well it can faithfully recapitulate human neurodevelopmental trajectory? To address

this question, Gordon et al. performed genome-wide epigenomic and transcriptomic analyses at different stages of cortical organoid differentiation and compared that to human brain development (Gordon et al., 2021). They found the transcriptional profiles of cortical organoids before 250–300 days are more like that of prenatal brains, while the transcriptional patterns of cortical organoids beyond 250–300 days are more like that of postnatal human brains. They also confirmed several known developmental milestones in cortical organoids such as the well-known switches of NMDA receptor subunits in the brain before and after birth (Paoletti et al., 2013), suggesting that cortical organoids, if successfully cultured for a long time, can model not only early neurodevelopment but also mid- to later-fetal stages (Gordon et al., 2021).

Cortical organoids, combined with scRNA-seq of tens of thousands of cells, provide an unprecedented opportunity to dissect the spatial and temporal early neuronal development in a cell-type-specific manner (Khrameeva et al., 2020; Pollen et al., 2019). Despite the single-cell transcriptomic similarities between brain organoids and developing brains (Tasic et al., 2016; Tasic et al., 2018; Zizhen Yao et al., 2020a), the functionality, i.e., electrophysiological properties of different types of neurons in brain organoids remain unexplored. This is largely due to the heterogeneity of different neuronal cells at variable stages of maturity. A promising approach is to generate a cell census map of cortical organoid neuronal subtypes with different functional dimensions by conducting a multimodal analysis of neurons in the 3D cortical organoid system (Personal communication with Dr. Zhiping Pang). To do so, a patch-seq technique (Bakken et al., 2020; Bardy et al., 2016; Cadwell et al., 2016; Cadwell et al., 2017; Chen et al., 2016; Fuzik et al., 2016; Scala et al., 2020; Zizhen Yao et al., 2020b) may be used to collect multimodal profiles, including electrophysiology, morphology, and transcriptomics from the same single cell of 3D organoids. The cellular taxonomy of neurons based on their functional, morphological, and transcriptomics features may be used as a general model to predict the functional identity of any neurons in 3D organoids.

Despite the advantages of using 3D organoids to model neurodevelopment, morphological variability and uneven cellular composition across organoids make the 3D organoid model more suitable for studying rare risk variants of highly penetrance rather than common risk factors of small effect sizes. Cortical organoids have been used to model autism- and SZ-associated 16p11.2 deletion and duplications (Urresti et al., 2021) and SZ-associated 22q11.2 deletion (Khan et al., 2020), illuminating temporal neurodevelopmental deficits in CNV-carriers that can be studied in 2D cell cultures. Using the method to generate cortical spheroids (Paşca, 2019), we also started to model the *SETD1A* LoF mutation associated with SZ, and the preliminary results showed that *SETD1A* LoF resulted in precocious neurogenesis (West et al., 2019). There are also attempts to model polygenic effects for SZ (Kathuria et al., 2020a) and BP (Kathuria et al., 2020b), each with cerebral organoids of 8 patents and 8 controls. However, the striking transcriptomic and phenotypic changes in SZ or BP organoids in these studies need to be interpreted cautiously, given the relatively small sample size and the known challenges of analyzing the bulk RNA-seq data and ascertaining the morphological differences in brain organoids.

4. Which cell type: disease relevance and region identify

Human iPSC can be differentiated into different brain cell types. For modeling neuropsychiatric risk variants, the cell type of interest can be informed by the known brain expression profiles and function of the risk gene and in general, by the disease-relevant cell types for each neuropsychiatric disorder.

Disease-relevant cell types and brain region identity for most neuropsychiatric disorders are not well defined. For instance, animal studies, human postmortem brain, and clinical brain imaging studies of SZ implicate almost every part of the brain, leaving the most disease-relevant or vulnerable cell types and their region identities unknown. Recent brain scRNA-seq transcriptomic profiling enables a global view of cell-type-specific gene expression patterns of each cell type/region at single-cell resolution (Habib et al., 2017; Zeisel et al., 2018). By mapping GWAS loci onto each specific brain cell type based on the cellular taxonomy of single-cell gene expression profiles, cortical inhibitory interneurons and excitatory neurons from the cerebral cortex and hippocampus (pyramidal and granule cells) as well as inhibitory medium spiny neurons (in the striatum) were found to be the most genetically vulnerable cell types for SZ (PGC3 et al., 2020; Skene et al., 2018). Across 265 cell types in the mouse central and peripheral nervous systems (Zeisel et al., 2018), glutamatergic (excitatory) neurons in the deep layers of the cortex, amygdala, and hippocampus showed the strongest enrichment for SZ heritability, which was followed by both inhibitory and excitatory neurons from the midbrain, thalamus, and hindbrain (PGC3 et al., 2020). In contrast, major depression disorder (MDD) and neurodegenerative disorders did not show such GWAS risk enrichment in these cell types (PGC3 et al., 2020; Skene et al., 2018). A more systematic analysis of all the most recent neuropsychiatric GWAS datasets with large samples would yield a more informative view of the most relevant brain cell types/regions for each neuropsychiatric disorder.

There has been no comprehensive neuropsychiatric GWAS risk enrichment analysis for iPSC-derived brain cell types to ascertain their disease relevance. Based on the GWAS risk enrichment analysis of open chromatin peaks and allele-specific open chromatin variants in iPSC-derived NPCs, glutamatergic, GABAergic, and dopaminergic neurons, we found all these cell types showed significant enrichment for SZ GWAS risk and to a less extent for BP and MDD (Zhang et al., 2020). Using Bulk RNA-seq data of iPSC-derived NPCs and microglia (iMG), our MAGMA analysis but not LDSC analysis showed enrichment of GWAS risk of SZ and BP in NPCs, while both analyses showed enrichment of GWAS risk of Alzheimer’s disease (AD) in the iMG (Butler Iii et al., 2020). A more systematic analysis of each iPSC-derived pure cell type in both 2D and 3D neural culture systems by scRNA-seq will better inform the genetic relevance of each iPSC-derived cell type to neuropsychiatric disorders.

It is worth noting that the disease-relevant cell type based on genome-wide gene expression and genetic association may not be applicable to some specific set of genes or pathways. For instance, for microRNA-137 (MIR137), a leading neuropsychiatric risk gene and a post-transcriptional master regulator, we conducted a cell type-specific gene set (MIR137 target genes) PRS analysis in both European and Han Chinese SZ samples (Yao et al.,

2021). Although the MIR137 target gene set expressed iPSC-derived glutamatergic neurons showed the greatest enrichment of SZ GWAS risk, which was consistent with the notion that glutamatergic neuron is the most disease-relevant cell types for SZ (PGC3 et al., 2020), we also found significant SZ risk enrichment in *MIR137* target genes expressed in iPSC-derived NPC or dopaminergic neurons (Yao et al., 2021). Specifically, we found that PRS derived from the predicted MIR137 target genes that are expressed in hiPSC-derived NPCs, GABAergic neurons, dopaminergic neurons, or glutamatergic neurons explains greater SZ risk variance than PRS derived from genes expressed in hiPSCs or other less relevant cell types (Yao et al., 2021). The cell-type-specific enrichment of SZ GWAS risk in different iPSC-derived cell types was further supported by an independent LDSC analysis (Yao et al., 2021).

It is also noteworthy that cell types not enriched for disease GWAS risk may still be important for some specific pathophysiological processes of SZ and other neuropsychiatric disorders. For instance, brain microglia or iPSC-derived microglia are not genetically vulnerable cell types for SZ (Butler Iii et al., 2020; PGC3 et al., 2020); however, dysregulation of synaptic pruning mediated by microglia has been hypothesized to be pathogenic to SZ (Sellgren et al., 2019; Sellgren et al., 2017). Excessive synapse pruning by microglia during adolescence may lead to the reduced synaptic density in the SZ brain, which is correlated with decreased gray matter thickness and reduced overall brain volume (Cannon et al., 2015; Glausier and Lewis, 2013; Lewis and Gonzalez-Burgos, 2008). The role of microglia in dysfunctional synaptic pruning in SZ was also partially supported by SZ GWAS: common SZ risk variants within the complement component 4 (C4) locus are associated with increased neuronal complement deposition and synapse uptake (Sellgren et al., 2019). Some other brain cell types may also play an important role: for example, astrocytes derived from BP patients are functionally less supportive of neuronal excitability and this effect is partially mediated by IL-6, suggesting a potential role of astrocyte-mediated inflammatory signaling in BP.

5. Which phenotype: disease-relevant cellular phenotypes

Disease-relevant specific cellular phenotypes for neuropsychiatric disorders remain largely undefined. Although for some brain cellular phenotypic changes have been observed for certain neuropsychiatric disorders, for instance, the reduced synaptic density in the SZ postmortem brain (Cannon et al., 2015; Glausier and Lewis, 2013; Lewis and Gonzalez-Burgos, 2008), the causal link between genetic risk factors, the observed cellular phenotypes, and clinical features of a neuropsychiatric disorder is lacking. Because of the neurodevelopmental aspects of autism and schizophrenia, compared to other neuropsychiatric disorders, the field has a better understanding of the postulated cellular phenotypes that are associated with neurodevelopmental abnormalities observed from postmortem brain studies and/or clinical brain imaging. The lack of defined disease-relevant cellular phenotypes poses a challenge to the iPSC modeling of neuropsychiatric disorders. On the other hand, well-powered studies of patient-specific iPSC lines, in combination with CRISPR gene editing to engineer specific disease risk variants, will help define disease-relevant cellular phenotypes and establish causal links with genetic risk factors.

Abnormal proliferation of iPSC-derived NPC has been implicated for autism and to a less extent, for SZ. The disease relevance of abnormal NPC proliferation is supported by known clinical features of autism, where either accelerated brain growth (i.e., macrocephaly) (Butler et al., 2005; Chawarska et al., 2011) or reduced brain size (i.e., microcephaly) can be seen in early brain development of some patients (Miles, 2011; van Bon et al., 2016). iPSC modeling microcephaly showed loss of NPCs and premature differentiation (Lancaster et al., 2013), while modeling macrocephaly showed rapid proliferation of NPCs (Marchetto et al., 2017). These opposite clinical phenotypes can be associated with different genetic risk factors, for instance, 16p11.2 duplication is associated with microcephaly while deletion is associated with large head size/macrocephaly (Steinman et al., 2016). However, iPSC modeling of 16p11.2 deletions and duplications did not show significant effects on NPC proliferation, rather recapitulated the opposite effects on neuron size and dendrite length (Deshpande et al., 2017), suggesting NPC proliferation may not be the only cellular phenotype associated with the early brain outgrowth in autism. Abnormal NPC proliferation has also been associated with SZ, but only in iPSC modeling. SZ iPSC-derived NPCs were found to have aberrant migration and increased oxidative stress (Brennand et al., 2015), while our iPSC-derived cortical organoids with SZ-associated *SETD1A* LoF mutation showed reduced NPC proliferation and precocious neurogenesis at early-developmental stage (West et al., 2019).

Most disease-associated cellular phenotypes are at the neuron level, often involving dendritic length, branches, synaptic puncta density, sodium/potassium/calcium channel activity, electrophysiology properties, and/or neural network activities. Dendrites and spines are the main neuronal structures that receive input from other neurons. For autism, both human postmortem brain and animal studies suggest a reduction of dendrite numbers and spine density (Martínez-Cerdeño, 2017). For schizophrenia, the most consistent findings are the reduced dendritic spine density and dendritic arborization in postmortem brains, and the accelerated adolescent gray matter reduction from brain imaging studies (Moyer et al., 2015). At the level of neuronal function, animal models of autism mutations reported both hyper- and hypoactivity associated with autism-like behaviors (Peça et al., 2011; Sacai et al., 2020; Schmeisser et al., 2012; Tabuchi et al., 2007; Won et al., 2012), while both pharmacology and genetic animal models of schizophrenia converge on hypofunction of glutamatergic synapse despite the reasonable skepticism as to how accurately animal behaviors can be reflective of schizophrenia (Coyle et al., 2020).

However, these cellular phenotypes of autism and SZ postulated from human postmortem brain, brain imaging, and animal studies were not fully recapitulated by the recent iPSC modeling of common or rare risk factors of both disorders (see above section “what to model”). For instance, contrary to the expected reduced dendritic complexities and synaptic function (Duan et al., 2019; Penzes et al., 2011), some iPSC modeling observed the increased dendritic complexities and neuronal hyperexcitability (Blizinsky et al., 2016; Forrest et al., 2017; Schrode et al., 2019; Yi et al., 2016; Zhang et al., 2020). These studied SZ risk variants include both common variation (e.g., a GWAS SNP at *M1R137* locus) (Forrest et al., 2017) with small effect sizes and rare risk alleles with high penetrance (e.g., 16p11 duplication or loss-of-function of *SHANK3*) (Blizinsky et al., 2016; Yi et al., 2016). Our recent modeling of a chromatin accessibility-altering common SZ risk variant

rs2027349 at the *VPS45* locus in isogenic NGN2-iNs further added another example that risk allele is associated with the increased dendritic complexity, synaptic puncta maturation, and neuronal firing rate (Zhang et al., 2021a). Such seemingly inconsistent cellular phenotypes may be the result of genetic pleiotropy across major psychiatric disorders (Ruderfer et al., 2018). Alternatively, hypo- and hyperfunction for the same disorder may reflect different temporal functional characteristics of neurons at different maturing stages. For instance, for patient-derived human hippocampal neurons carrying a rare autism-associated missense mutation A350V in gene *IQSEC2,* the immature dentate gyrus (DG) granule neurons are extremely hyperexcitable, while the aged neurons are hypoexcitable (Brant et al., 2021). However, neural maturity may not explain some of the observed increase of dendritic complexities and synaptic puncta in SZ neurons, e.g., the effect of the common risk allele at *MIR137* locus (Forrest et al., 2017), which was confirmed by a mouse model of the MIR137 risk allele (i.e., with haploinsufficiency of MIR137) (Cheng et al., 2018). Finally, among other plausible interpretations, the reported both neural hyperfunction (Blizinsky et al., 2016; Forrest et al., 2017, a; Schrode et al., 2019; Yi et al., 2016; Zhang et al., 2020) and hypofunction (Duan et al., 2019; Penzes et al., 2011) in SZ iPSC models provide further support for a neuronal homeostatic model of neuropsychiatric disorders where either excess or inadequate synaptic signaling output may contribute to pathophysiology (Landek-Salgado et al., 2016; Ramocki and Zoghbi, 2008).

As a possible mechanistic link to dendritic and synaptic dysfunction as described above for SZ and autism, the abnormal microglia-mediated synapse pruning may also be considered as a cellular phenotype relevant to neurodevelopmental disorders. For SZ, the hypothesis is that excess synaptic pruning could trigger the disease during the active period of synapse elimination in adolescence; while for autism, human and animal studies imply a deficit of pruning that may lead to excessive synaptic connections (Sakai, 2020). The idea has gained empirical support from iPSC modeling of synaptic pruning in SZ (Sellgren et al., 2019; Sellgren et al., 2017). With an in vitro model of microglia-mediated synapse engulfment, the excessive synaptic pruning in SZ lines was found to result from abnormalities in both microglia-like cells and synaptic structures (Sellgren et al., 2019). However, although the SZ-associated C4 allele is correlated with synapse uptake (Sellgren et al., 2019), a causal relationship between the *C4* risk variant and the increased synapse engulfment is lacking. Moreover, because the activated-microglia-conditioned medium has been found to alter metabolism differentially in SZ iPSC-derived cortical interneurons, neural synaptic deficit may play a major role in microglia-mediated synaptic pruning (Park et al., 2020). Therefore, it remains uncertain whether the increased phagocytosis by microglia is a cellular phenotype genetically relevant to SZ.

6. What next: challenges, opportunities, and new research frontier

iPSC modeling of neuropsychiatric risk factors is becoming more popular in the field. However, some limitations of the model and challenges remain to be appreciated: (1) The sample size is relatively small in almost all the iPSC modeling studies, while it is becoming clear that donor genetic background and iPSC clonal variation are common confounding factors. (2) Modeling common risk variants and genes remains challenging simply because functional interpretation and causal inference of noncoding risk variants

are not as straightforward as protein-coding variants. (3) Disease risk variants may only manifest their functional effects at a specific cellular state and in a context-specific manner, e.g., neural activation-dependent effects. (4) Nonnuclear DNAs such as mitochondrial DNA (mtDNA) may play a significant role in the etiology of neuropsychiatric disorders.

6.1. Scaling up the iPSC modeling

Confounding factors in iPSC modeling often arise from the line-to-line variation due to the effects of different donor genetic backgrounds, iPSC clonal-to-clone variation originated from cellular reprogramming and/or iPSC cell passaging processes, and technical variations resulted from cell culturing and neuronal differentiation procedures. Compared to 2D culture, 3D organoids show even more variations during the lengthy culture process (months). For instance, although the cell type diversity is quite producible across organoids (Velasco et al., 2019), the cellular composition and subtype specification vary substantially between organoids and across protocols, especially at later stages of cortical organoid maturation (Bhaduri et al., 2020; Velasco et al., 2019). Although line-to-line variation can be mitigated by using CRISPR editing-based isogenic approach to enable the experimental comparison virtually on the same genetic background between isogenic pairs, the phenotypic expressivity can still be influenced by the genetic background of each donor. Furthermore, the iPSC clonal variation often makes transcriptomic data difficult to interpret, even with isogenic design and in a setting with multicenter and cross-lab validation (Pak et al., 2021). As such, when the sample size is small, these potential confounding factors can substantially limit the interpretation of molecular and cellular phenotypes associated with psychiatric risk variants in iPSC modeling.

It is becoming increasingly recognized that the iPSC modeling needs scaling up, both on the number of iPSC lines to be used and the variant numbers to be studied. The current situation in iPSC modeling is somewhat reminiscent of the early stage of the candidate gene association study of neuropsychiatric disorders when a small sample size and a small number of interrogated genetic markers often yield false-positive associations and evidence hanging in the balance (Sanders et al., 2008). A larger sample size can alleviate the experimental variations and produce more rigorous results. However, scaling up iPSC modeling is currently not only associated with higher cost but also needs conceptual and technical innovations on how to delineate the molecular and cellular phenotypes more effectively for a large number of iPSC lines and risk variants/genes (Fig. 2).

To scale up the number of iPSC lines, one straightforward way is to culture individual iPSC lines in separate wells on a multi-well plate, followed by high-content imaging of neuron morphology, synaptic maturation, and electrophysiological properties (Fig. 1)a. With this setting, for each individual line, a co-culture system may be used to differentially label excitatory (e.g., by GCaMP) and inhibitory (e.g., by RCaMP) neurons, which will enable the morphometric analyses of different types of neurons simultaneously. The high-content imaging system (e.g., ImageXpress) can auto-segment the images, which can be analyzed for dendritic complexity and synaptic puncta density using built-in methods or some customized machine learning-based methods such as *Intellicount* (Fantuzzo et al., 2017). Taking advantage of high-performance Ca^{2+} sensors (GCaMP and RCaMP) for imaging

neuronal activity (Chen et al., 2013; Dana et al., 2019), the cellular electrophysiology property of both types of neurons can also be assayed by high-throughput Ca^{2+} imaging with a two-photon microscope.

Alternatively, iPSC sample scaling up can be done by an innovative approach “cell village” (Mitchell et al., 2020). With this setting, 10s to 100s iPSC lines can be co-cultured together in a cell culture dish and differentiated into neurons together, followed by cell sorting to groups neurons based on a specific cell surface marker or antigen (i.e., cellular phenotype) and then by Census-seq to associates cellular phenotypes to donors’ genotypes in cell “villages” (Fig. 1)b. Although this approach measures cellular phenotypes in cells from many donors simultaneously, it would be challenging to establish a customized “village” where all the iPSC lines may grow in balance, i.e., without a few overgrowing others. Furthermore, with many co-cultured lines, cell non-autonomous effects may confound the analysis and data interpretation. Nonetheless, “cell village” has been proved to be effective in mapping common genetic variants affecting some cellular phenotypes such as SMN protein levels in spinal muscular atrophy (SMA) (Mitchell et al., 2020).

In a sense, “cell village” (and census-seq) also scales up the variant number, because it assays the effect of many common alleles on a specific phenotype (e.g., SMN protein level) at a cell population level (Mitchell et al., 2020). However, it is still an association-based approach to establish a correlation between genotype and phenotype rather than directly modeling function/causal variant *en masse.* In a proof-of-concept experiment, Cederquist et al. carried out a multiplex iPSC screening, in which 30 isogenic lines carrying different autism mutations are pooled in a single dish and differentiated into the prefrontal cortex (PFC) lineages to test early developmental hypotheses of autism (Cederquist et al., 2020). With PFC neurogenesis as a cellular phenotype for pooled screening, mutations were sub-grouped into those that enhance or suppress neurogenesis (Cederquist et al., 2020), providing a framework to disentangle genetic heterogeneity associated with autism and identify converging molecular and cellular phenotypes of diverse disease variants. However, the number of modeled variants here remains small, and the way to individually CRISPR-engineer the mutations would not be suitable to further scale up the number of assayed variants.

To substantially increase the number of variants/genes (100s or 1000s) to be modeled, pooled, or multiplex CRISPR/Cas9 SNP/gene editing or epigenome editing will be needed. The editing will be mediated by low-MOI (multiplicity of infection) lentivirus infection to introduce single guide RNAs (sgRNAs) into each cell, followed by molecular and phenotypic screening at a single-cell resolution (F 2c). For modeling LoF mutation, CRISPR/Cas9 editing can be used to systematically create small indels in protein-coding regions through non-homologous end joining (NHEJ) repair of double-strand breaks (DSBs) (Ran et al., 2013), resulting in protein-truncating mutations. Alternatively, LoF mutation can be efficiently generated by introducing premature protein stop codon using CRISPR cytosine base editors (CBE) without creating DSBs (Cuella-Martin et al., 2021; Xu et al., 2021). To mitigate the cell-toxic DSBs and off-target editing of DNAs associated with CRISPR/Cas9 editing (Ran et al., 2013), or the possible off-target RNA editing associated with CBE editing (Cuella-Martin et al., 2021; Xu et al., 2021), CRISPRi (Holtzman and

Gersbach, 2018) or its more effective version, CRISPRoff (Nunez et al., 2021) can be used to transcriptionally repress the expression of the sgRNA-targeted genes by rewriting the epigenomic state without changing DNA sequences (i.e., epigenome editing). Compared to modeling LoF mutation, precisely editing many risk SNPs in iPSCs remains challenging due to the low homology-directed repair (HDR) efficiency in CRISPR/Cas9 editing (Ran et al., 2013). However, the rapidly evolving high-efficiency SNP base editing system (CBE or ABE) (Cheng et al., 2021; Cuella-Martin et al., 2021; Hanna et al., 2021; Richter et al., 2020) may enable massive parallel assessment of hundreds or thousands of SNPs in iPSCs.

For the above-described pooled editing of many risk variants/genes, it is essential that sgRNA barcodes individual cells for molecular and cellular phenotyping at single-cell resolution. Molecular phenotyping (e.g., transcriptomic level) is relatively easy because scRNA-seq can distinguish individual cells barcoded by single gRNAs thus allowing to assess SNP/gene editing effect on cis-target gene expression or transcriptomic changes. However, cellular phenotyping can be challenging depending on whether the cellular phenotype can be subject to cell sorting. For a phenotype that can be distinguished by cell sorting, cells that underwent the pooled editing can be sorted into two groups and the effects of genetic variants can be analyzed as described for CRISPRi pooled screening (Nunez et al., 2021). For morphological phenotype such as neuron dendritic branches, a combination of Pro-Code technique to barcode each gRNA/edited cell (Wroblewska et al., 2018) with CODEX multiplex imaging of single cells (Goltsev et al., 2018) may be needed (Fig. 2c). In this setting, each gRNA, and thus each cell infected by the gRNA, will be tagged by a combination of 3 or more genetic barcodes detectable as protein tags (Pro-Codes) (Wroblewska et al., 2018). Then, each pro-code barcoded cell can be imaged sequentially for each protein tag using the CODEX technique that also allows interrogating the immunofluorescence staining of cell-specific markers (e.g., PSD95) as part of the CODEX detection panel (Goltsev et al., 2018). The obtained single-cell imaging data can be used for ascertaining the cellular phenotypic effects of each risk variant/gene in a pooled or multiplexed CRISPR SNP/gene editing.

6.2. Functional and mechanistic interpretation of noncoding risk variants

Functional interpretation of noncoding variants is important, because most GWAS risk variants of neuropsychiatric risk variants, like for other complex disorders, are in the noncoding part of the genome. Furthermore, as whole genome-sequencing data in large samples become available, it is conceivable that some rare noncoding variants may be found associated with disease similarly to those rare coding variants identified by SCHEMA (Singh et al., 2020). However, it is challenging to study the function of common noncoding risk variants in primary human tissues and at early development stages, particularly for brain disorders. Although brain eQTL, chromatin-accessibility QTL (caQTL) and chromatin interaction (Hi-C) data from PsychENCODE (Gandal et al., 2019; Gandal et al., 2018; Li et al., 2018; Rajarajan et al., 2018; Wang et al., 2018) are instrumental for prioritizing functional noncoding risk variants, iPSC-based models can provide additional regulatory dimension at early neurodevelopment stage that may not be captured by brain QTL mapping. Furthermore, because iPSC models are amenable to genetic manipulation, they

can provide mechanistic insight on how noncoding risk variants may affect disease risk genes.

eQTL can inform noncoding regulatory variants that are associated with one or more target genes in *cis* or in *trans.* The only eQTL mapping study in an iPSC model is for dopaminergic neurons differentiated from 215 iPSC lines, a sizable sample for iPSC study (Jerber et al., 2021). Leveraging the scRNA-seq profiling at a single-neuron resolution, eQTLs were identified for both relatively pure dopaminergic neurons and another intermediate subtype of cells at different differentiation stages. Although iPSC-derived eQTL maps mimic in vivo GTEx brain eQTL maps, about 2366 eQTL were detected only in iPSC models. Of the 1284 eQTL colocalized with known neurological trait risk loci, 46% are not found in the GTEx catalog (Jerber et al., 2021), highlighting the added value of mapping eQTLs in iPSC models. Identifying eQTLs in other brain cell types relevant to major neuropsychiatric disorder, e.g., glutamatergic and GABAergic neurons co-cultured and differentiated from a moderate number of iPSC lines, is warranted.

There has been no available caQTL dataset for iPSC-derived neurons. Chromatin accessibility precedes gene transcription and can help interpret regulatory noncoding variants. Similar to the concept of caQTL, we have recently mapped putatively functional noncoding variants that showed differential allelic chromatin accessibility, as we designated as allele-specific open chromatin (ASoC), in NPC, glutamatergic (including both NPC-derived and NGN2-induced), GABAergic and dopaminergic neurons derived from 20 iPSC lines (Zhang et al., 2021a; Zhang et al., 2020). Because ASoC directly compares the two alleles within an individual, it is expected to be a more sensitive assay of chromatin-regulating variants than traditional QTL analysis using cross-sample variation (i.e., caQTL) (Calderon et al., 2019; Zhang et al., 2020). ASoC SNPs frequently alter expression (Forrest et al., 2017; Zhang et al., 2020) but act upstream of transcription, thus complementing eQTL analysis. Importantly, neuronal ASoC SNPs, compared to open chromatin peak regions, exhibited much stronger enrichment for SZ risk variants (Zhang et al., 2021a; Zhang et al., 2020). The neuronal ASoCs were partially driven by altered transcription factor binding, overrepresented in brain gene enhancers and eQTLs, and frequently associated with distal genes through chromatin contacts. We also identified abundant neuronal open chromatin peaks not detected in brains. Our ASoC analysis in iPSCs highlights ASoC as a functional mechanism of noncoding neuropsychiatric risk variants, providing a powerful framework for identifying disease causal variants and genes.

eQTL mapping is association-based and does not directly inform which is the functional SNP among its LD proxies (R^2 >0.8). ASoC may directly point to a functional SNP but still needs orthogonal functional validation as we demonstrated (Zhang et al., 2020). Massive parallel reporter assay (MPRA) provides a powerful approach to systematically test the regulatory potential of tens of thousands of noncoding GWAS risk variants, thus enabling to cross-validate or screen for the putatively functional variants prioritized from QTL mapping and GWAS. MPRA has been used to test GWAS risk variants of neuropsychiatric and neurological disorders in non-neuronal cells (Myint et al., 2019; Myint et al., 2020), where both alleles of each SNP along with the ~ 100-bp flanking sequence at each side are synthesized and cloned next to a minimal promoter, sequence-based barcode, Kozak

consensus sequence, and the *GFP* gene, into a construct for transducing or transfecting mammalian cells. The level of expression of the barcodes in the RNA of both alleles will be compared to determine whether the targeted sequences of both alleles differentially drive gene expression. Among several variations of MAPR such as STARR-seq (Arnold et al., 2013) and capSTARR-seq (Vanhille et al., 2015), a lentivirus-based MPRA approach, as described by Gordon et al. (2020), may be most suitable for systematically efficiently infecting neuronal cells. Despite its limitation of only testing SNP function on a very short surrounding sequence without the intact genomic sequence context, MPRA in iPSC-neurons will be invaluable in providing direct functional evidence for noncoding risk variants of neuropsychiatric disorders.

To gain mechanistic insight on disease GWAS associations, it is imperative to tie the functional noncoding risk variants to their *cis*- or *trans*-regulated target genes. While eQTL mapping can help make the connection, chromatin contact mapping (Hi-C) provides direct evidence for physical interaction between a risk variant and its target gene(s). With iPSC-derived NPCs, neurons, and astrocyte-like glial cells as in vitro models of human brain development, Rajarajan et al. mapped genome-wide chromatin contacts, or "three-dimensional genome" (3DG), in different cell types using Hi-C (Rajarajan et al., 2018). It was found that many SZ risk loci showed 3DG connections with genes outside the risk loci, representing long-range distal gene regulation and expanding the putative disease risk genes by 50 to 150% (Rajarajan et al., 2018). Although most 3DG connections involved in these disease risk loci still need orthogonal validation, the concept of long-range regulation was independently confirmed by a recent mapping of cis-regulatory chromatin contacts in neural cells using promoter capture-HiC (Song et al., 2019). Hundreds of thousands of long-range cis-interactions between promoters and distal promoter-interacting regions, many of which are cell type-specific, were identified in iPSC-derived excitatory neurons, lower motor neurons, hippocampal dentate gyrus-like neurons, and in primary astrocytes, enabling to link regulatory elements to their target genes (Song et al., 2019).

In support of the widespread long-distance cis-target genes, our focused study of a SZ risk variant rs2027349 showing strong ASoC near *VPS45* found that CRISPR editing of rs2027349 altered the expression of *VPS45, lncRNA AC244033.2,* and a distal gene, *Clorf54,* in human neurons. Notably, we found all three cis-target genes of rs2027349 contribute to the cellular phenotype change in a non-additive manner, which was supported by chromatin contacts between the risk variant and all three cis-target genes, including the distal *Clorf54* (Zhang et al., 2021a). The compound effects of all three cis-genes in the same GWAS locus (*VPS45*) (Zhang et al., 2021a) resemble the synergistic transcriptional effects of multiple SZ risk loci that were recently demonstrated in iPSC-derived neurons (Schrode et al., 2019), albeit the lack of 3DG chromatin contacts between those different SZ risk loci (Rajarajan et al., 2018). Thus, iPSC modeling provides mechanistic insight on how noncoding risk variants function and confer disease risk.

6.3. Cellular state- or context-specific effects of risk variants

Context-specific regulatory variants can unmask hidden disease heritability, which has been well demonstrated for immune disorders (Calderon et al., 2019; Farh et al., 2015;

Kim-Hellmuth et al., 2017; Lee et al., 2014; Ramos-Rodriguez et al., 2019). Many risk variants of immune disorders are functional only in stimulated cells; for instance, cytokine stimulation of pancreatic β-cell unmasks abundant novel regulatory sequences, and remarkably, only stimulated enhancers are enriched for type 1' GWAS variants (Ramos-Rodriguez et al., 2019). For neuropsychiatric disorders, the commonly used postmortem brains tissues (e.g., by PsychENCODE) (Amiri et al., 2018; Gandal et al., 2018; Li et al., 2018; Rajarajan et al., 2018), cannot capture the effects of disease variants in specific biological contexts, e.g., developmental stages and responses to stimuli (Calderon et al., 2019; Farh et al., 2015; Kim-Hellmuth et al., 2017; Lee et al., 2014) (Calderon et al., 2019; Farh et al., 2015; Kim-Hellmuth et al., 2017; Lee et al., 2014). In mice, neuronal activity in response to neurotransmitters leads to Ca^{2+} influx, activating early response genes (ERGs; e.g., *FOS*) and late response genes (LRGs; e.g., *BDNF*), regulating dendritic growth, synapse development, and neuronal plasticity (Yap and Greenberg, 2018). Some cytokines (e.g., IL-4, IL-17, and IFN-r) also affect neuronal activity, leading to neurodevelopmental abnormality and behavioral changes in animal models (Filiano et al., 2016; Reed et al., 2020; Ribeiro et al., 2019; Vogelaar et al., 2018). At a molecular level, neural activity in mouse brain induced drastic alterations of OCRs, accompanied by expression changes of 2000–5000 genes within 4–6 h (Fernandez-Albert et al., 2019; Su et al., 2017).

iPSC-derived neurons provide a cellular model suitable for testing neural activity-dependent changes and the effects from disease risk variants. In vitro, a variety of stimuli like membrane-depolarizing levels of potassium chloride (KCl) can induce neuronal activity that mimics the in vivo effects of visual and social experiences, stress, or drugs of abuse in mice (Yap and Greenberg, 2018). With a small sample size (iPSC lines from 4 SZ cases vs. 4 controls), Roussos et al. identified >1000 differentially expressed genes in iPSC-derived neurons in response to KC1 depolarization (Roussos et al., 2016). The robust activity-dependent gene expression may be partially due to activity-dependent secretion of catecholamines—dopamine (DA), norepinephrine (NE), and epinephrine (Epi), which was found elevated in SZ cases (Hook et al., 2014). A recent comprehensive activity-dependent transcriptional and epigenetic profiling of iPSC-derived GABAergic neurons further identified a genome-wide profile of activity-dependent enhancers and promoters (Boulting et al., 2021), and the inducible promoters were found significantly enriched for heritability of ASD, suggesting the sequence variants within activity-inducible promoters of developing human forebrain GABAergic neurons contributes to ASD risk (Boulting et al., 2021**).**

To systematically identify neuronal activity-dependent functional variants in major neuronal cell types relevant to neuropsychiatric disorders, we have designed an experiment that combined the co-culture of iPSC-derived excitatory and inhibitory neurons and scRNA/ATAC-seq in about 100 iPSC lines (See NIH RePORTER, PI: Duan) (Fig. 3). iPSC lines of different donors in the co-culture can be demultiplexed (Kang et al., 2018) based on their genotypes. Stimulated neurons co-cultured with glial cells will be assayed by scRNA-seq and by scATAC-seq (or by using 10 x Genomics' Multiome kit), followed by mapping of stimulation-specific eQTLs and ASoC SNPs or caQTLs different time points of neural activation (Fig. 3). The neural activity-dependent regulatory variants will complement our

previous ASoC (Zhang et al., 2020) and existing brain eQTL datasets (Amiri et al., 2018; Gandal et al., 2018; Girdhar et al., 2018; Psych et al., 2015; Rhie et al., 2018; Wang et al., 2018), expanding the repertoire of regulatory neuropsychiatric risk variants that may affect chromatin accessibility and gene expression only in activated/stimulated hiPSC neurons.

6.4. Dysfunctional mitochondria in neuropsychiatric disorders

There is a growing body of evidence that supports the role of mitochondrial dysfunction in neuropsychiatric disorders (Andreazza and Nierenberg, 2018; Ben-Shachar, 2017; Kato et al., 2011; Kim et al., 2019; Morava and Kozicz, 2013; Pei and Wallace, 2018). The reasoning behind the hypothesis was that since the mitochondria are the powerhouse of the cells, and the brain consumes a significant proportion of the bodies energy evident in the abundance of mitochondria in brain cells, individuals whose mitochondria functions suboptimally are more prone to stress-associated pathologies, thus, are more susceptible to neuropsychiatric disorders (Andreazza and Nierenberg, 2018; Kim et al., 2019; Morava and Kozicz, 2013; Pei and Wallace, 2018). Multiple mtDNA deletions have been associated with BD and SZ (Kato, 2011; Mancuso et al., 2008) or depression (Gardner et al., 2003). Some reports also show a higher prevalence of neuropsychiatric disorders in people with mitochondrial diseases compared to patients with other metabolic disorders and their relatives or the general population (Grover et al., 2006; Kato, 2011; Levey et al., 2020; Oexle and Zwirner, 1997). In one mtDNA association study on 50,000 individuals, including cases of eleven different diseases as well as controls, SZ was among the top diseases that had a significant association with certain mtDNA polymorphisms (Hudson et al., 2014). Moreover, alterations in complex I and complex IV in the respiratory chain could be found in SZ patients that had mtDNA deletions in their brain tissues (Whitehurst and Howes, 2022). In addition to evidence from studies on human patients and cells, multiple studies on mice support the theory that mitochondrial dysfunction may be directly involved in the pathology of neuropsychiatric disorders (Hovatta et al., 2010; Kato et al., 2011; Salim et al., 2010).

More recently, the role of mitochondrial dynamics in iPSCs has become of interest (Sercel et al., 2021), and iPSC models of dysfunctional mitochondria in neuropsychiatric disorders are being used to understand the pathogenic aspects that cannot be explained by the nuclear DNA (Zilocchi et al., 2020). Compared to other neuropsychiatric disorders, more focus has been given to studying mitochondrial dysfunction of SZ using iPSC models (Ni and Chung, 2020). iPSC-derived neural cells from SZ patients showed alterations in oxidative phosphorylation (OXPHOS) and ROS levels (Brennand et al., 2015; Li et al., 2019; Li et al., 2021b; Ni et al., 2020), disruption in mitochondrial membrane potential and respiration (Robicsek et al., 2013) (Brennand et al., 2015), and affected biochemical and protein networks in mitochondria in neurons (Li et al., 2019; Ni et al., 2020; Robicsek et al., 2013; Sullivan et al., 2019). One study found that co-culturing iPSC-derived neurons from SZ patients with activated microglia results in disruption in mitochondrial function that was not observed in controls (Park et al., 2020). Specific genetic risk factor of SZ, e.g., 22qdeletion, has also been linked to dysfunctional mitochondria in patient-specific iPSC models (Li et al., 2019). However, it remains to be established whether mitochondria dysfunction is the causal factor or consequence of neuropsychiatric disorders.

Despite the lack of a causal mechanistic link between dysfunctional mitochondria and neuropsychiatric disorders, iPSC modeling may help establish mitochondria as a potential therapeutic target for some neuropsychiatric disorders (Marazziti et al., 2012; Pei and Wallace, 2018). For instance, studies on animals and cellular models found that some current mood-stabilizing drugs and antidepressants, including lithium, valproate, and selective serotonin reuptake inhibitors, are known to affect mitochondrial energy metabolism and antioxidant activity in patients and animal models (Jou et al., 2009; Wu et al., 2013; Zilocchi et al., 2020). Other studies of SZ patients' iPSC-derived neurons found that stimulating mitochondrial biogenesis by treating cells with bezafibrate and antioxidants (e.g., α-lipoic acid and acetyl-L-carnitine) can reverse mitochondrial deficits and abnormal arborization in SZ patients' neurons (Li et al., 2021b; Ni et al., 2020; Park et al., 2020). Even some over-the-counter antioxidant supplements, such as mitoquinones, show anxiolytic and neuroprotective effects (Cocheme et al., 2007; Filiou and Sandi, 2019; Nussbaumer et al., 2016; Snow et al., 2010). In this regard, it is noteworthy that treating iPSC-derived neurons of familial Parkinson's disease (PD) patients with small molecules that target mitochondrial stress can rescue PD-relevant neuronal deficits (Cooper et al., 2012).

Studying mitochondrial dysfunction in iPSCs also has general implications for iPSC modeling of neuropsychiatric risk factors. This is because mtDNA is prone to mutations, which can affect the cell's survival, health, and pluripotency of iPSCs (Sercel et al., 2021; Tian et al., 2021). To that point, only very few known mtDNA polymorphisms have been studied in hiPSCs (Sercel et al., 2021), which means that controlling cell culture conditions, proliferation, and differentiation in hiPSCs with mtDNA heteroplasmy (and related mutations) is a necessary subject of investigation. Resolving such issues is important for minimizing any mtDNA mutation-caused potential poor reproducibility and functional discrepancies from different iPSC clones in disease modeling. New advances in mtDNA gene editing (Mok et al., 2020) can open the door to better modeling mitochondrial dysfunction in hiPSCs.

7. Conclusion

Tractable and reproducible experimental models are pivotal for bridging the gap between genetic findings and disease biology. For modeling genetic risk factors of neuropsychiatric disorders, because of the inherent limitation on drawing causal inferences about psychiatric disease mechanisms, it is critical to clearly define the research question, carefully select the most appropriate experimental system, and rigorously design a well-powered study (see guidelines in a recent review (Alexander Arguello et al., 2019)). With iPSC-derived 2D and 3D models, studying both common and rare risk variants of neuropsychiatric disorders has provided valuable mechanistic insights on how genetic risk factors contribute to disease risks. However, the exact cellular phenotypes and causal molecular mechanisms for each neuropsychiatric disorder remain poorly understood. Most iPSC modeling studies focus on single variants/genes and use a small number of iPSC lines, which may have contributed to the inconsistencies across studies. To improve the robustness and reproducibility of disease variant modeling, it is critical to implement or develop novel methods to scale up the number of iPSC lines and disease risk variants in a systematic manner. Enough cell lines and variants, in combination with cutting-edge CRISPR/Cas9 gene editing and

single-cell multi-omics methods, will enable the field to identify convergent molecular and cellular phenotypes that are relevant to a specific disorder or reflective of cross-disorder genetic pleiotropy. It is equally important to further improve the fidelity of iPSC models, especially the brain organoids, by minimizing the stochastic developmental processes and increasing the spatial and temporal control to better recapitulate the in vivo neurodevelopment and brain function. To account for the functional effects from "missing heritability," it is imperative to consider cellular state or context-specific regulation, gene x environmental interaction, and mtDNA mutations. Finally, neuropsychiatric disorders are polygenic, or even "omnigenic" where thousands of peripheral genes confer disease liability by perturbing a core set of genes (Boyle et al., 2017), it is thus increasingly clear that most risk genes function as gene networks controlled by master regulators (MRs) such TFs (Doostparast Torshizi et al., 2019). Instead of modeling individual risk variants/genes, network perturbation of MRs and other core genes by multiplex CRISPR/Cas9 editing in iPSCs may be needed to more faithfully recapitulate the molecular and cellular phenotypes that are relevant to neuropsychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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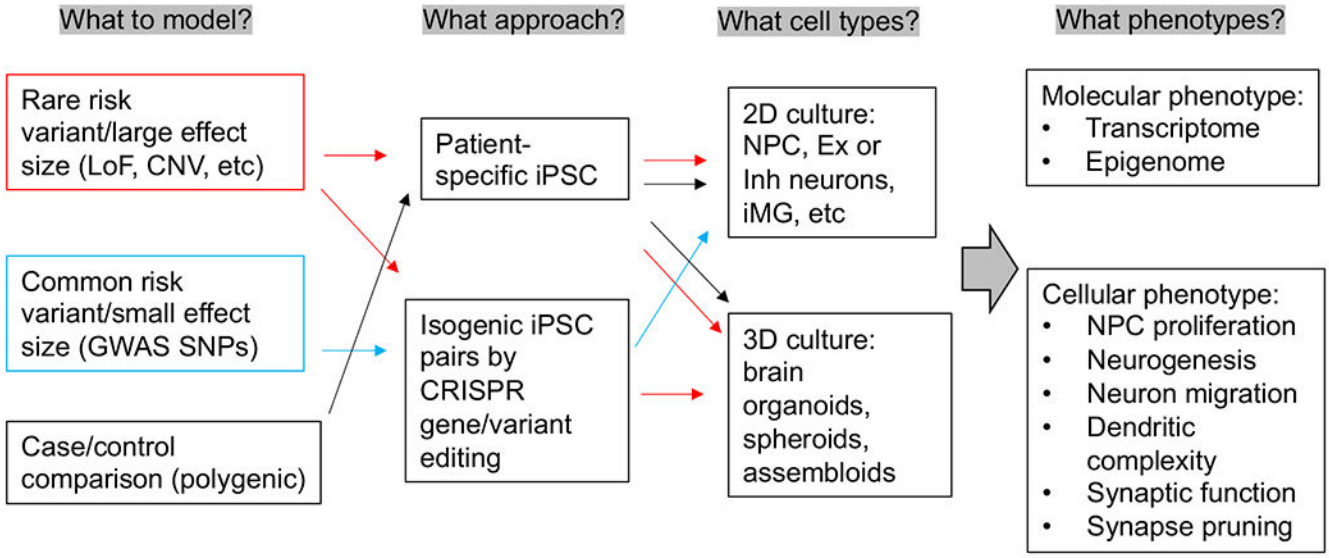

Fig. 1.

The type of neuropsychiatric risk variants and the disease relevant cellular phenotypes in iPSC modeling. Red, blue or black arrow indicates iPSC modeling for rare variants/CNV, common variants, or polygenic risk factors, respectively. LoF = loss of function; CNV = copy number variants; Ex = excitatory neurons; Inh = inhibitory neurons; iMG = iPSC-derived microglia. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

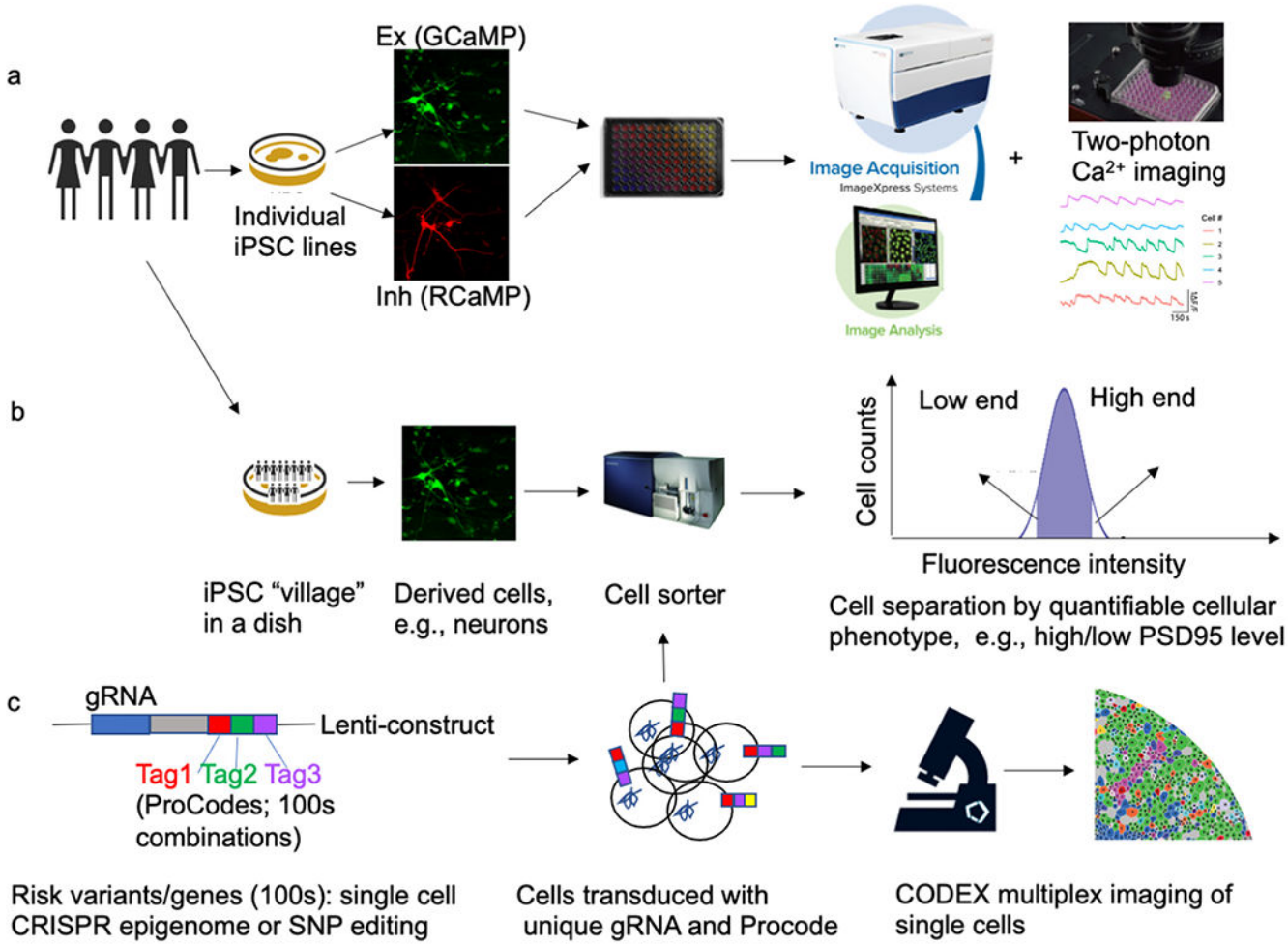

Fig. 2.

Approaches for scaling up the number of iPSC lines and/or genetic risk variants/genes as well as cellular phenotyping. (a) Individually cultured iPSC lines on multi-well plates assayed by high-content imaging, (b) iPSC lines co-cultured on a dish, i.e., a "cell village" approach, combined with a pooled phenotype screening. (c) Scaling up the number of genetic risk variants for iPSC modeling by employing a ProCode approach combined with CODEX multiplex imaging at single-cell resolution.

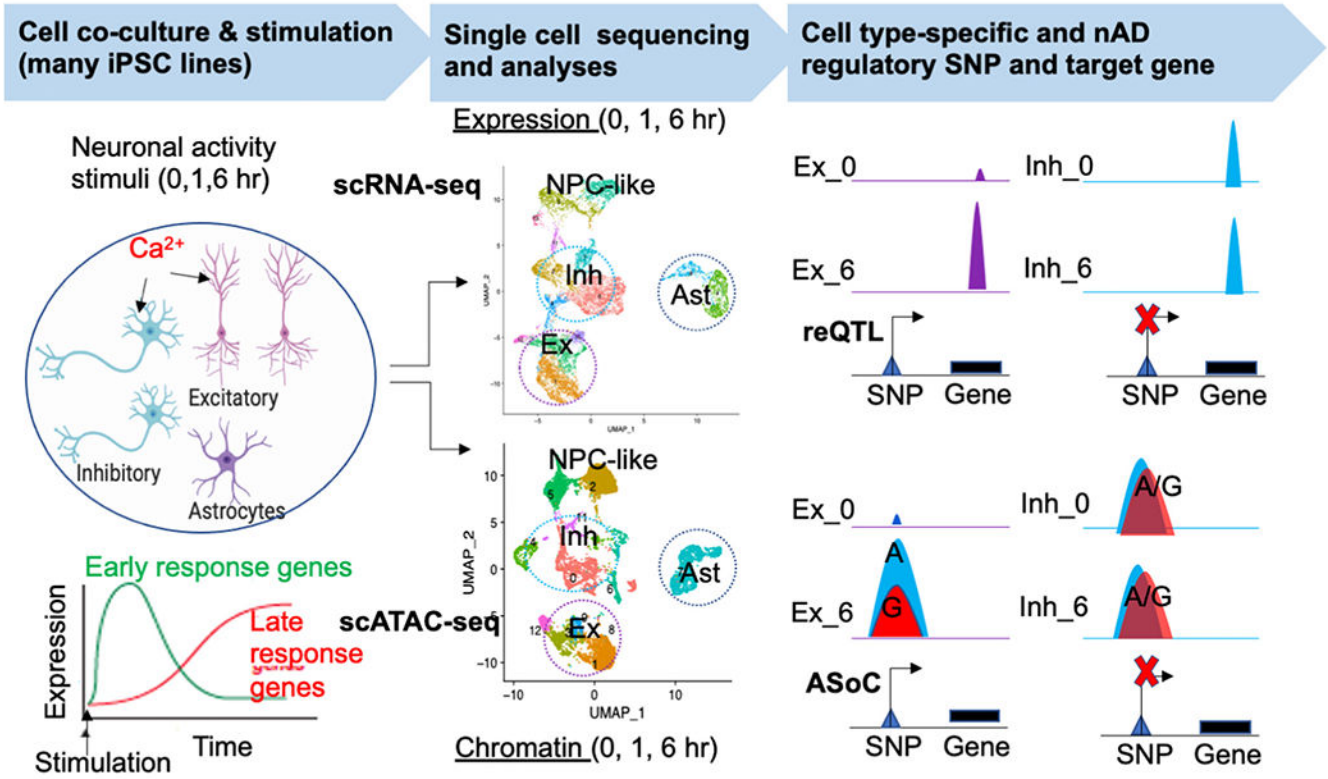

Fig. 3.

A schematic design of assaying neural activity-dependent functional noncoding SNPs in a co-culture system. The co-cultured excitatory and inhibitory neurons can be stimulated by KCl, followed by scATAC-seq/scRNA-seq to separate Ex and Inh neurons, astrocytes (Ast), and residual NPCs (middle). Cell type-specific regulatory SNPs that affect gene expression (reQTL) and chromatin (ASoC) are identified (right).

Table 1

hiPSC models of neuropsychiatric risk variants (only studies with clearly defined disease risk variants and cellular phenotypes are listed).

Author/year	Ref	Disease	Risk variant/gene	Perturbation	Sample size	Brain cell type	Cellular phenotypes
Urresti 2021	34433918	ASD	16p11.2 CNV	Comparative	3 × DEL & 3 × DUP + 3 ctrls	Organoids	Excess of neurons and depletion of NPCs in DELs; Organoid size recapitulates macrocephaly and microcephaly phenotypes observed in the patients.
Roth 2020	33169669	ASD	16p11.2 CNV	Comparative	10 DEL/3 DUP + 4 ctrls	Cortical neurons	Significant correlation between transcription modules and clinical phenotypes in 16pDS patients.
Deshpande 2017	29212016	ASD	16p11.2 CNV	Comparative	3 × DEL & 3 × DUP + 4 ctrls	Neurons	Increased soma size and dendrite length in 16p DEL, which were decreased in 16p DUP neurons. Both exhibited reduced synaptic density.
Deneault 2019	30747104	ASD	16p11.2 DEL, *NRXN1*Δ/+	Comparative; CRISPR/Cas9	14 ASD + 11 ctrls	Glutamatergic neurons	Consistent spontaneous network hyperactivity for *CNTN5*−deficient or *EHMT2/UBE2I*-variant.
Carbonell 2019	31388001	ASD	*ANKS1B*	Comparative	2 cases + 2 ctrls	Neurons	Loss of *ANKS1B* led to altered synaptogenesis and neurodevelopment.
Deneault 2018	30392976	ASD	*FF2/FMR2, ANOS1, ASTN2*, etc.	CRISPR/Cas9; isogenic	10 isogenic hiPSC lines	Excitatory neurons	Electrophysiological deficits were distinct for different mutations. Consistent reduction of synaptic activity and reduced sEPSC frequencies.
Avazzadeh 2021	34525970	ASD	*NRXN1*α	Comparative	3 NRXN1α+/− + 5 ctrls	Cortical neurons	Higher sodium currents and action potential, and accelerated depolarization time.
Zaslavsky 2019	30911184	ASD	*SHANK2* DEL (R841X)	CRISPR/Cas9	2–4 isogenic lines	Cortical neurons	Increased synapse numbers and longer dendrites. Hyperconnectivity and increased sEPSC frequency.
Wang 2021	bioRxiv	ASD	*SHANK3*	CRISPR/Cas9; isogenic	3 mutants + 3 ctrls	Cortico-striatal organoids	Smaller organoids with fewer and smaller neurons. Fewer synapsin1/SHANK3-containing excitatory synaptic puncta and high excitability.
Gouder 2019	30643170	ASD	*SHANK3* (E809X, Q1243X, G1271Afs*15, L1142Vfs*153)	Comparative	4 SHANK3-het ASD + 3 ctrls	Pyramidal cortical neurons	Significant reduction in dendritic spine densities and whole spine and spine head volumes.
Chiola 2021	33558651	ASD	*SHANK3* hemizygosity	CRISPR/Cas9; xenografting	4 PSC lines + 4 ctrls	Astrocytes & glut neurons	Impaired AMPA-mediated synaptic transmission, dendritic arbors, and spines in the mouse cortex.
Fink 2021	34538422	ASD (AS)	15q11-q13 DUP	Comparative	4 Dup + 6 ctrls	Excitatory & inhibitory neurons	Increased excitatory synaptic activity, dendritic density, and action potential. Decreased inhibitory synaptic transmission.
Utami 2020	32653109	ASD (FXS)	*FMR1*	CRISPR/Cas9	4 FXS + 3 ctrls (1 isogenic)	GABAergic & glutamatergic	Abnormal FXS neural rosette formation. Overall impairment of electrophysiological network activities.

Author/year	Ref	Disease	Risk variant/gene	Perturbation	Sample size	Brain cell type	Cellular phenotypes
Das Sharma 2020	32560741	ASD (FXS)	*FMR1*	CRISPR/Cas9; comparative	3 FXS + 3 ctrls (1 isogenic)	Cortical neurons	No observed differences in the intrinsic properties of FXS neurons. Shorter and more frequent spontaneous action potential firing in FXS neurons.
Achuta 2017	27411166	ASD (FXS)	*FMR1*	Comparative	4 FXS + 3 ctrls	NPCs and neurospheres	Intracellular calcium response to the mGluR agonist DHPG was augmented in FXS NPCs.
Lutz 2020	32522805	ASD (PMS)	*SHANK3* deficiency	Comparative	5 PMS + 3 ctrls	Neurons/myotubes	Shortened *Z*-discs and severe impairment of acetylcholine receptor clustering in PMS myotubes.
Roessler 2018	30456368	ASD (PMS)	22q13.3 DEL	CRISPR/Cas9; comparative	3 DEL & 2 CRISPR + 1 ctrl	NPCs & cortical neurons	Impairment of neuronal maturation and reduced overall activity in 22q DEL. reduced protein levels of SHANK3, JIP2, DCX, and NeuN.
Trujillo 2021	33501759	ASD (RTT)	*MECP2* LoF (Q83X, K82 frameshift)	CRISPR/Cas9; drug screening	2 mutants + 2 ctrls	Neurons & organoids	Nefiracetam and PHA 543613 reversed the cytologic neuropathology in *MECP2*-KO neurons, increased calcium activity in mosaic neurospheres.
Chen 2021	32851591	ASD (RTT)	*MECP2*	CRISPR/Cas9 mutagenesis	2 mutants + 3 isogenic ctrls	Cortical neurons	RTT neurons lack electrophysiological maturation. Spine density is impaired. Synaptic transmission abnormalities were observed in *MECP2* KD neurons.
Gomes 2020	33363173	ASD (RTT)	*MeCP2*: R255X(XX), *MeCP2*:Q83X(XY)	Comparative	2 MeCP2 RTT + 4 ctrls	Forebrain organoids	Premature development of the deep-cortical layer neurons, low NPCs, and altered calcium dynamics. Impaired interneuron migration in RTT forebrain organoids.
Xiang 2020	32526163	ASD (RTT)	*BRD4, MECP2* (c.397C > T, C.808C > T, c.916C > T)	CRISPR/Cas9	5 RTT + 2 ctrls (1 isogenic)	Interneurons and brain organoids	Abnormal increases in BRD4 binding cause the abnormal transcription of mutant MeCP2 in RTT interneurons.)
Nott 2016	27428650	ASD (RTT)	*MECP2* (R306C)	CR1SPR/Cas9; comparative	1 mutant + 1 isogenic ctrl	NPCs	Deficits in HDAC3 and FOXO recruitment and gene expression. CRISPR editing rescued the impaired HDAC3-FOXO-mediated phenotype in NPCs.
Williams 2014	24419315	ASD (RTT)	*MECP2*	Comparative	3 RTT + 3 ctrls	Astrocyte & neuron	Mutant astrocytes had adverse effects on the morphology and function of wild-type neurons.
Ananiev 2011	21966470	ASD (RTT)	*MECP2* (R306C, T158M, R294X, V247X)	CRISPR/Cas9; comparative	4 MeCP2 + 4 ctrls	Neurons	RTT neurons were smaller than their isogenic controls.
Kim 2011	21807996	ASD (RTT)	*MECP2* (T158M, Q244X, E235fs, R306C, X487W)	Comparative	5 RTT + 5 ctrls	NPCs & neurons	Neuronal maturation deficits.
Marchetto 2010	21074045	ASD (RTT)	*MECP2* (1155del32, R306C, Q244X, T158M)	Comparative	4 RTT + 5 ctrls	NPCs & neurons	RTT NPCs had normal proliferation. RTT neurons had reduced glutamatergic synapse numbers and abnormal morphologies.
Panagiotakos 2019	31868578	ASD (TS)	*CACNA1C*	Comparative	3 TS + 3 ctrls	NPCs & neurons	SATB2+ neurons were less abundant while CTIP2+ neurons were more abundant.
Paşca 2011	22120178	ASD (TS)	*CACNA1C*	Comparative	2 TS + 3 ctrls	NPCs & neurons	Deficient Ca^{2+} signaling, decreased lower cortical layers, abnormal tyrosine hydroxylase

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							expression, and increased production of norepinephrine and dopamine.
Nadadhur 2019	30581017	ASD (TSC)	*TSC1* (2249G > A), *TSC2* (1563dupA/H522T)	Comparative	2 TSC + 3 ctrls	Neurons & oligodendrocytes	Increased dendritic branching and network activity. Oligodendrocytes had increased proliferation and decreased maturation.
Becker 2020	32929080	ASD, MICPCH	*CASK* (c. 1296 + 1 G > T), *CASK* (Xp11.4 DUP)	Comparative	2 mutants + 2 ctrls	Neurons	Altered presynaptic development and affecting their excitatory/inhibitory balance.
Jiang 2019	30135510	BP	*TRANK1* (rs9834970T > C, rs906482G > A)	Comparative; drug treatment	2 BP + 8 ctrls	NPCs & neurons & astrocytes	The NPCs with the risk allele of rs9834970 had lower baseline *TRANK1* expression.
Yoshimizu 2015	25403839	MDD, BP, SZ	*CACNA1C* (rs1006737 G > A)	Comparative	10 BP + 4 SZ + 2 MDD + 8 unaffected	Neurons	L-type VGCC current density, as well as mRNA expression of *CACNA1C*, were increased.
Wen 2014	25132547	MDD, SZ	*DISC1*	Comparative	4 DISC1-het (2 isogenic) + 4 ctrls	NPCs & cortical neurons	Synaptic vesicle release deficits in forebrain neurons. Dysregulated expression of many synaptic genes associated with psychiatric disorders.
Sundberg 2021	34006844	SZ	16p11.2 CNV	CRISPR/Cas9; isogenic	3 isogenic lines & 1 x 16p11.2 ctrl	Dopaminergic neurons (DA)	16p DUP showed deficits in neuronal differentiation. 16p DEL had increased soma size and hyperactivity, which can be rescued by RHOA inhibition (Rhosin).
de Vrij 2018	29302076	SZ	*CSPG4* (c.391G > A [p.A131T])	Comparative	3 SZ + 3 related ctrls	OPCs	Aberrant cellular morphology, and myelination potential.
Srikanth 2018	30410030	SZ	*DISC1, UNC5D*	CRISPR/dCas9-VPR for KD	2 mutants + 2 isogenic ctrls	Neurons	DISC1 mutations did not seem to alter cell fate, presynaptic protein expression, or electrophysiological activity. Reduced neurite outgrowth.
Shrode 2019	31548722	SZ	*FURIN* (rs4702), *SNAP91, TSNARE1*	CRISPR/Cas9; CRISPRa/i	4 CRISPR-edited + 4 ctrls	NPCs, glut & GABAergic	Reduced neurite length and firing rates in rs4702 GG neurons. sEPSCs frequency/ amplitude increased in *SNAP91* CRISPRa (decreased with CRISPRi).
Forrest 2017	28803920	SZ	*MIR137* (rs1198588)	CRISPR/Cas9	1 isogenic pair (2 clones)	Glutamatergic neurons	The Risk allele is associated with lower *MIR137* expression, increased dendritic complexity, and synaptic puncta positive for GluA1 and PSD95.
Pak 2021	34035170	SZ	*NRXN1*	Patient-specific & TALENs	3 patients + 3 ctrls; 3 edited	Neurons	A deficit in spontaneous & evoked synaptic events responses, synaptic paired-pulse depression. Impaired synaptic function regardless of genetic background.
Zhang 2021	bioRxiv	SZ	*VPS45*, AC244033.2, or *C1orf54* (rs2027349)	CRISPR/Cas9; isogenic	2 isogenic pairs (2–3 clones)	Excitatory neurons	Risk allele A is associated with increased dendritic complexity, synaptic puncta density, and hyperactivity; cis-regulated all three genes with synergistic effects.
Li 2021c	34009292	SZ (DGS)	22q11.2 DEL	Comparative	8 × DEL + 6 ctrls	Neurons	Reduced OXPHOS activity and ATP levels.

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Li 2019	31740674	SZ (DGS)	22q11.2 DEL, *MRPL40*	CRISPR/Cas9; comparative	4 × DEL & 1 KO + 5 ctrls	Neurons	Reduced levels of mitochondrial-encoded proteins, ATP, and electron transport chain activity.
Khan 2020	32989314	SZ (DGS), ASD	22q11.2 DEL, *DGCR8*	CRISPR/Cas9; comparative	12 × 22q11DS + 11 ctrls	Cerebral cortical organoids	Defects in spontaneous neuronal activity and calcium signaling. *DGCR8*+/− neurons show similar neuronal dysfunction and behavior to 22q11DS neurons.
Flaherty 2019	31784728	SZ (psychotic)	*NRXN*α	Comparative	4 NRXN1α+/− + 4 ctrls	Glutamatergic & GABAergic	Aberrant and differentially-expressed NRXN1 isoforms. Deficits in neuronal activity depending on expressed NRXN1α isoforms in a genotype-dependent manner.
Li 2021d	33833053	SZ, ASD	16p11.2 CNV, *CD47*	Comparative	11 SZ and ASD lines + 3 ctrls	NPCs & OPCs	*CD47* is overexpressed in 16p11.2 DEL contributing to reduced phagocytosis.
Johnstone 2018	30401811	SZ, GAD/MDD	16p13.11 DUP, *TSC2* (16:2115634:C/T)	Comparative	3 × 16p13.11 DUP + 5 ctrls	NPC & organoids	16p13.11 DUP NPCs had proliferation deficits and cerebral organoids were smaller and had altered radial glial progenitor cell division fates.