2024-04-15

Unravelling the Genetic Basis of Schizophrenia

Clara Casey

John F. Fullard

Roy D. Sleator

Gene 902 (2024) 148198

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Unravelling the genetic basis of Schizophrenia

Clara Casey [a,b,c,d], John F. Fullard [b,c,d], Roy D. Sleator [a,*]

[a] Department of Biological Sciences, Munster Technological University, Bishopstown, Cork, Ireland
[b] Center for Disease Neurogenomics, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States
[c] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States
[d] Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States

ARTICLE INFO

Edited by: Maria P. Ivshina

Keywords:
Schizophrenia
Omics technologies
Genetics
Epigenetics

ABSTRACT

Neuronal development is a highly regulated mechanism that is central to organismal function in animals. In humans, disruptions to this process can lead to a range of neurodevelopmental phenotypes, including Schizophrenia (SCZ). SCZ has a significant genetic component, whereby an individual with an SCZ affected family member is eight times more likely to develop the disease than someone with no family history of SCZ. By examining a combination of genomic, transcriptomic and epigenomic datasets, large-scale 'omics' studies aim to delineate the relationship between genetic variation and abnormal cellular activity in the SCZ brain. Herein, we provide a brief overview of some of the key omics methods currently being used in SCZ research, including RNA-seq, the assay for transposase-accessible chromatin with high-throughput sequencing (ATAC-seq) and high-throughput chromosome conformation capture (3C) approaches (e.g., Hi-C), as well as single-cell/nuclei iterations of these methods. We also discuss how these techniques are being employed to further our understanding of the genetic basis of SCZ, and to identify associated molecular pathways, biomarkers, and candidate drug targets.

1. Introduction

Schizophrenia (SCZ) is a severely debilitating mental illness that affects 1 % of the population worldwide (Wright et al., 2000). However, despite being first described by Stengel (1960), more than six decades ago, as "a severe disturbance of the ego" caused by "a number of conditions", SCZ has remained a relatively poorly characterized chronic mental health disorder. Lacking a suitable molecular diagnostic test, or reliable biomarker, an SCZ diagnosis can still only be made based on a qualified analysis of psychiatric symptoms (American Psychiatric Association, 2013).

Structural neuroimaging and functional analyses have framed SCZ as a disorder of abnormal neuronal activity leading to impaired communication between cells and brain regions (Ragland et al., 2007). Indeed, neuroimaging of individuals with SCZ has revealed structural deficits in the prefrontal, superior temporal, and medial temporal brain regions, including reduced grey matter volume and disrupted white matter integrity (Karlsgodt et al., 2010; Wright et al., 2000). Functional magnetic resonance imaging (fMRI) analysis has shown abnormalities in working memory and cognitive control in the learning circuits of the frontotemporal region, as well as impaired activity of cortical midline brain regions during self-processing (Gur and Gur, 2010; Javitt, 2009).

However, despite decades of research, the true etiology of SCZ remains poorly characterized. As such, the development of pathophysiology-based diagnostic tools and functional therapeutic treatments have remained stubbornly elusive.

Current treatment regimens include the prescription of antipsychotic drugs; in particular dopamine D2 receptor antagonists that block dopamine release in the midbrain to successfully treat positive SCZ symptoms (Howes and Kapur, 2009). However, this treatment approach

Abbreviations: SCZ, Schizophrenia; ATAC-seq, assay for transposase-accessible chromatin with high-throughput sequencing; Hi-C, high-throughput chromosome conformation capture; fMRI, Functional magnetic resonance imaging; GWAS, Genome wide association studies; PGC, The Psychiatric Genomics Consortium; SCHEMA, Schizophrenia Exome Meta-Analysis Consortium; SNVs, single nucleotide variations; SNPs, single nucleotide polymorphisms; eQTLs, expression quantitative trait loci; caQTLS, chromatin-accessible quantitative trait loci; OCRs, Open Chromatin Regions; CNVs, Copy Number Variants; PTVs, Protein Truncating Variants; scRNA, single-cell RNA; snRNA, single-nuclei RNA; snRNAs, small nucleolar RNAs; H3K4, Histone H3 Lysine 4; ASD, autism spectrum disorder; PFC, prefrontal cortex; NMDA, N-methyl-D-aspartate; iPSC, induced pluripotent stem cells; lncRNA, long non-coding RNA; miRNA, microRNA; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; DRD2, dopamine receptor D2; 3C, chromosome conformation capture.

* Corresponding author.
E-mail address: Roy.sleator@mtu.ie (R.D. Sleator).

https://doi.org/10.1016/j.gene.2024.148198
Received 1 September 2023; Received in revised form 7 December 2023; Accepted 19 January 2024
Available online 22 January 2024

is largely ineffective for negative or cognitive symptoms of SCZ (Fig. 1). If left untreated, these symptoms can lead to premature death from health complications, suicide, violent criminal activity, or substance-use disorder (Charlson et al., 2018; Tripathi et al., 2018). Indeed, it is proposed that individuals with SCZ are up to six times more likely to commit a violent crime than healthy individuals (Fazel et al., 2009; Fleischman et al., 2014). As such, the emotional and financial burden of SCZ on the individual, their family, and society, is considerable. Although the scientific community has strived for decades to elucidate the molecular basis of SCZ, the cellular and molecular pathogenesis of the disease remains largely unknown due to the genetic diversity of the disease and challenges associated with studying an organ as inaccessible and complex as the human brain.

2. Research objectives and scope

Herein, we review the current state of the art in relation to the genetic basis of SCZ. Contributing factors including genetics, epigenetics, and specific epigenetic regulators (e.g., histone epigenetic modification, DNA methylation, post-transcriptional regulation of non-coding RNA (nc-RNA)) are discussed. Furthermore, advanced techniques used to measure genetic and epigenetic changes are reviewed, including RNA-seq, ATAC-seq, Hi-C, and multi-omic assays, both at a bulk and single-cell level.

Key observations include recognition of the polygenic nature of the disorder, the impact of common and rare variants, and the role of non-coding variation in epigenetic regulation are discussed. Additionally, the transformative power of single-cell analysis in SCZ research is described; highlighting core mechanisms affected, including glutamatergic signaling, synaptic plasticity, and brain development.

The aim of this review is thus to outline approaches to map the intricate molecular landscape of SCZ; paving the way for future diagnostic and therapeutic developments.

2.1. Genetics

With the rise of the 'omics' era in the past two decades, the SCZ research field has witnessed a technological transformation. Genome wide association studies (GWAS) and whole exome sequencing studies have led to novel discoveries that have contributed significantly to our understanding of disease susceptibility and onset (Dobbyn et al., 2018; Singh et al., 2020, 2022). GWAS can be applied to large cohorts to identify genomic variants that are associated with increased risk for a disease or a particular trait (Sullivan et al., 2018). To date, perhaps one of the most impactful contributions to the field of SCZ research was the establishment of The Psychiatric Genomics Consortium (PGC) and Schizophrenia Exome Meta-Analysis Consortium (SCHEMA); two complementary landmark genetic studies of more than 320,400 people (Singh et al., 2020; Sullivan et al., 2018). Together, these milestone studies provided the necessary statistical power to confidently call risk variants, even if their respective effect sizes are small (Singh et al., 2022; Trubetskoy et al., 2022). These efforts led to the identification of rare single nucleotide variations (SNVs), and common single nucleotide polymorphisms (SNPs) that include expression quantitative trait loci (eQTLs; i.e. SNPs that affect levels of gene expression), chromatin-accessible quantitative trait loci (caQTLS; SNPs that regulate gene expression by modulating chromatin structure), Copy Number Variants (CNVs) and Protein Truncating Variants (PTVs). Some of these rare and common variants were found in both disease and healthy cohorts, suggesting that the presence of these SNPs does not necessarily lead to onset of disease (Trubetskoy et al., 2022). Complicating matters even further is the fact that the absence of these risk variants does not guarantee that an individual will not develop SCZ (reflective of the fact that environmental factors, such as trauma and malnutrition, likely play a role in some cases (Stilo and Murray, 2019). Genetic analysis has also revealed that rare and ultra-rare susceptibility variants in SCZ patients are linked to increased burden of SCZ when compared to more common SNPs (Korn et al., 2008; Singh et al., 2022).

To date, 287 variants have been associated with increased risk of developing SCZ. As such, SCZ is considered a polygenic disorder, caused by the interaction of multiple SNPs affecting several different genes (International Schizophrenia Consortium et al., 2009; Trubetskoy et al., 2022). These genetic markers, while shedding light on potential risk factors, lay the groundwork for exploring the intricate interplay between

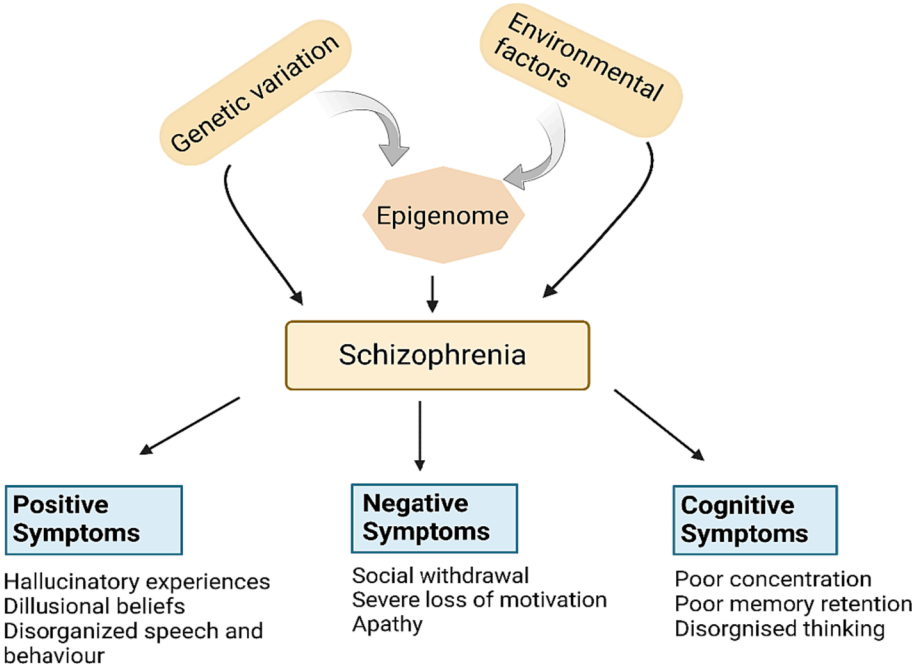

Fig. 1. Overview of Schizophrenia risk factors and symptoms. Genetic variation plays a significant role in SCZ. Common and rare single nucleotide polymorphisms (SNPs) contribute to the heritability of SCZ. A combination of SNPs and environmental factors can lead to the onset of SCZ in a process that is theorized to affect the epigenomic regulation of neurodevelopmental processes, leading to positive, negative and/or cognitive symptoms.

genes and their regulatory mechanisms. Most of the SNPs associated with SCZ are commonly found in both individuals with the disorder and those without it, which means that their individual influence on the risk of developing SCZ is usually minor. The impact of the rare and ultra-rare risk variants can vary wildly; increasing the likelihood of developing SCZ from 1 % to as high as 60 % (Singh et al., 2020). However, these variants account for only 24 % of the heritability of SCZ – a disease that has an estimated heritability of 80 % (Hilker et al., 2018). As such, the "missing heritability" of SCZ remains the focus of intense investigation. The vast majority (>90 %) of the identified risk variants are non-coding, i.e., they have no direct impact on protein sequence or structure/function (Roussos et al., 2014). As we delve deeper into understanding the genetic landscape of SCZ, it becomes evident the static genome alone cannot fully explain the complexity of the disorder. Instead, increasing evidence suggests that the genetic variation associated with SCZ disrupts the function of *cis*-Regulatory Elements (CREs), including promoters and enhancers (Roussos et al., 2014). This dynamic interplay between genetics and gene regulation shapes the landscape of SCZ susceptibility and development. CREs play critical roles in the spatiotemporal regulation of gene expression and are often cell-type specific in their function (Panigrahi and O'Malley, 2021). As such, mutations that lead to suboptimal CRE function may only affect specific cell types or subtypes. Given the cellular heterogeneity of the human brain, to fully understand the complex molecular underpinnings of SCZ one must consider approaches that focus on analysis at the cellular level (either at the resolution of specific cell types, e.g., neurons and/or glia, or using more agnostic approaches that interrogate individual cells, irrespective of their identity or function). This is particularly pertinent in cases where the affected cells are in a minority, information from which would be lost in bulk tissue assays.

2.2. Single-cell versus bulk analysis in SCZ

Bulk data analysis aims at drawing comparisons of genomic, transcriptomic, proteomic and metabolic cellular content across all cell types in the specimen being examined (Henry et al., 2010; The ENCODE Project Consortium, 2012). However, this type of analysis can mask critical cellular heterogeneity information of seemingly identical cells, or different cells, within a tissue (Colman-Lerner et al., 2005; das Neves et al., 2010). There are also some technical challenges, for example, isolation methods to enrich for specific cell types of interest, particularly so when studying frozen specimens, where cell surface markers are often lost upon thawing. Single-cell approaches provide a means to agnostically capture data from a sample of all cells or nuclei in a given specimen. In support of this, single-cell analysis has revealed substantial genetic heterogeneity among different cell populations, urging researchers to focus instead on specific cell populations (Chambers et al., 2019). While 10X Genomics developed one of the most widely used approaches for creating scRNA/snRNA-seq libraries using microfluidics (Ding et al., 2020), there is an increasing number of scRNA/snRNA-seq alternatives coming to the market, some of which are instrument-free approaches (e.g., Seq-Well (Aicher et al., 2019; Gierahn et al., 2017).

However, despite its potential, single-cell analysis faces certain limitations. These include the cost associated with single-cell technologies and reagents which can be a significant barrier (Angerer et al., 2017), restricting accessibility. Furthermore, large single-cell analysis can be computationally challenging, given the substantial resources and time required to analyze data from millions of single cells (Andrews et al., 2021; Sarkar and Stephens, 2021). Notwithstanding these limitations, single-cell gene expression analysis is especially useful when studying brain disease, as the diversity of, for example, neuronal cell types in the brain is vast when compared to those in the spinal cord (Alkaslasi et al., 2021; Peng et al., 2021). Non-neuronal, i.e., glial cells, including oligodendrocytes, astrocytes and microglia compose 20 % to 40 % of cell types in the brain and are molecularly and functionally diverse (Domingues et al., 2016; Zhang and Barres, 2010). The brain has 86 billion neurons, divided into three broad classes (sensory neurons, motor neurons and interneurons) with each class containing many distinct subtypes (Hawrylycz et al., 2012; Song et al., 2021). The brain's function is extremely complex and highly regulated, with hundreds of different neuronal cell types playing diverse functions, both across and within brain regions (Peng et al., 2021). Single-cell analysis allows identification of populations of cells that are transcriptionally distinct, affect important developmental neuronal pathways, and, ultimately, have different functions in healthy and disease states (Pollen et al., 2014). Single-cell gene expression analysis has revealed substantial differences in expression of important SCZ genes when compared across cell types and brain regions (Dong et al., 2022; Hoffman et al., 2019). This powerful study confirmed previous findings whereby genes associated with SCZ are enriched in pyramidal neurons and medium spiny neurons (Skene et al., 2018). Another noteworthy study, encompassing 140 individuals, identified dysregulated genes specific to 25 distinct brain cell types, predominantly within excitatory neuronal subpopulations and also within astrocytes (Ruzicka et al., 2022). Employing Hi-C-coupled-MAGMA (H-MAGMA), the researchers assigned non-coding SNPs to their target genes, unveiling an overlap of common and rare variants associated with SCZ risk in select cell types. Furthermore, a convergence of rare and common variants was observed in other neuronal subpopulations. These findings underscore the potential of single-cell omics studies as a promising approach to gaining more in-depth pathophysiological insights into the effects of SCZ GWAS loci (Trubetskoy et al., 2022).

Astrocytes, the predominant glial cell type in the brain, are important contributors to the etiology and pathogenesis of SCZ (Trindade et al., 2023). Functioning as key regulators of synaptic, neuronal, and network activities, astrocytes have a broad range of functions, encompassing critical roles in neuroprotection, neurodevelopment, synaptic plasticity, and immune functions (Jäkel and Dimou, 2017). Astrocytes play pivotal roles in pathways disrupted in SCZ, including glutamatergic signaling and synaptic plasticity. Numerous studies underscore their involvement in the onset of cognitive and olfactory symptoms, linking astrocytic dysfunction to aberrant glutamate signaling, demyelination and synaptic function (Bernstein et al., 2015; Roussos et al., 2011; Trindade et al., 2023). Further exploration of the molecular underpinning of SCZ has revealed dysregulated NMDAR signaling in astrocytes as a significant correlate with pathophysiology (Cohen et al., 2015; Jääskeläinen et al., 2013). Single-cell analysis has in recent times provided more insight into the various astrocyte populations and their functions within different brain regions, offering possible solutions for advancing diagnosis and treatment in SCZ (Batiuk et al., 2020).

Furthermore, a proposed role for microglia – the resident immune cells of the brain - in SCZ was recently demonstrated by Gober and colleagues, who identified morphological, spatial, and density differences between microglia from SCZ cases and a healthy cohort (Gober et al., 2022). Microglia represent approximately 10 % of the cells in the brain, so attempting to study their genetic/transcriptomic landscape in bulk tissue is challenging. Identifying molecular biomarkers in specific cell populations from individuals with SCZ might ultimately lead to the discovery of novel diagnostic blood biomarkers and treatment targets. In the context of complex brain diseases, the upsurge of single-cell methods suggests that the technology is finally catching up with the problem (Mu et al., 2019; Olah et al., 2020; Piwecka et al., 2023).

2.3. Epigenetics

Of the SCZ-associated genetic risk loci identified to date, >90 % of them reside in non-coding regions of the genome (Ripke et al., 2013). This large SCZ-associated variation in non-coding DNA and RNA has given rise to the hypothesis that neuroepigenetic mechanisms may explain the so-called missing heritability in SCZ (Akbarian, 2014). Epigenomics, and epitranscriptomics, is focused on investigating changes in gene expression caused by chemical modifications in DNA and proteins

in the nucleosome (Dixon et al., 2012). DNA is packaged with histone proteins into chromosomes in the nuclei, in molecular complexes known as nucleosomes (Luger et al., 1997). Compacted DNA in this form is known as chromatin, and its 3D structure and interactions with other proteins in the nucleus play a vital role in regulating gene expression, in what are known as epigenetic processes. Epigenomic regulation can be achieved through different mechanisms such as non-coding RNA/RNA interference, chromatin structure alterations, histone modification or DNA methylation (Fig. 2). Each of these mechanisms varies in terms of its effect size and stability (Samantara et al., 2021). Effect size refers to the magnitude or extent of the impact that a particular mechanism has on epigenomic regulation, while stability pertains to the long-term persistence of the regulatory effects exerted by each mechanism (Felling et al., 2012). Neuroepigenomic mechanisms contribute to the dynamic plasticity of the brain, meaning that the epigenetic landscape changes throughout development and in response to environmental stimuli (Felling and Song, 2015). Synaptic plasticity is thought to be the basis of long-term learning and memory formation (Willard and Koochekpour, 2013). The core affected pathways in the pathogenesis of SCZ are glutamatergic signaling, synaptic plasticity and brain development. Disruptions to these processes may account for the morphological differences seen in neurons of diseased tissue and, ultimately, the disease pathology (Harrison and Weinberger, 2005). When nuclei corresponding to different populations of neurons (GABAergic and glutamatergic) and glia (oligodendrocytes and other glia; microglia and astrocytes) were subjected to chromatin structure profiling, *via* ATAC-seq, the resulting data indicates that accessible (i.e., potentially functional) regions of chromatin in glutamatergic neurons are enriched for SCZ associated risk variants (Hauberg et al., 2020), thereby providing additional evidence for the role of this class of neurons in SCZ.

2.4. Non-coding RNA epigenetic regulation.

The existing literature underscores significant alterations in non-coding RNA profiles among individuals with SCZ, thereby contributing to dysregulated gene expression in these individuals (Dave and Khalili, 2010; Guo et al., 2022; Ni et al., 2021). Studies have consistently reported changes in various non-coding RNA species, including microRNA (miRNA), small nucleolar RNA (snoRNA), and long non-coding RNA (lncRNA), within the brains of SCZ-affected individuals (Bond et al., 2009; S. Chen et al., 2016; Ragan et al., 2017a).

Elevated miRNA levels in the brain, relative to other body parts, imply a crucial role within the central nervous system (CNS). These small RNA molecules modulate gene expression by binding to mRNA transcripts, exerting influence over their stability, translation, transport, and degradation functions (O'Brien et al., 2018). Within the brain, miRNA target genes have been associated with neurodevelopment, synaptic function, and neuroinflammation (Dave and Khalili, 2010; Im and Kenny, 2012; Kumar et al., 2022). Altered miRNAs are notably overrepresented among the SCZ risk genes (Tian et al., 2018). Of the 120 SCZ-associated genes from the PGC GWAS (Sullivan et al., 2018; Trubetskoy et al., 2022b), eight were identified as targets of the dysregulated miRNAs (Ragan et al., 2017b). These genes, implicated in metabolic processes and neurodevelopment – particularly, calcium signaling – signify potential key players in SCZ pathology. While the precise mechanisms through which miRNAs contribute to SCZ remain under investigation, elucidating their role in the pathophysiology of SCZ holds promise for advancing our understanding of the disorder at the

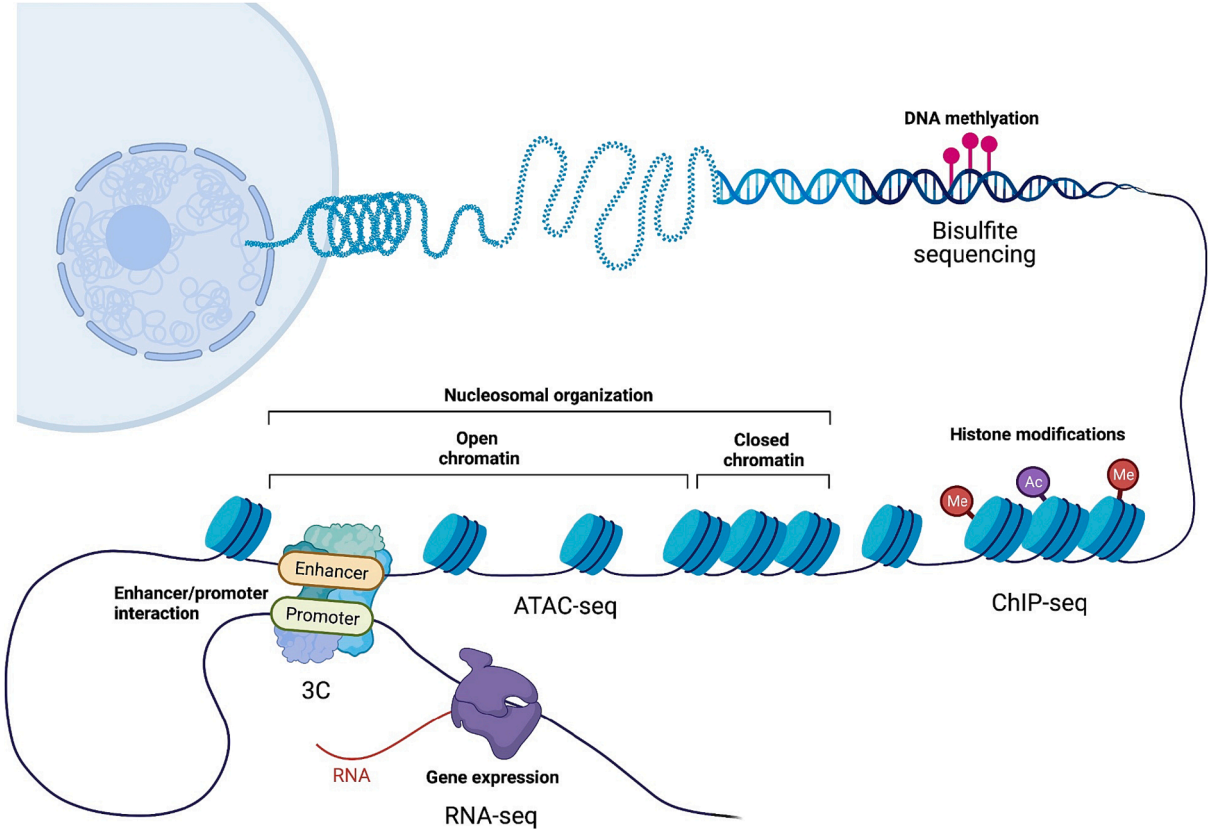

Fig. 2. Methods of Transcriptome and Epigenome analysis. Genomic DNA is modified by DNA methylation to control gene expression. DNA methylation is a type of epigenetic modification that can be profiled by bisulfite sequencing methods. Further epigenetic modifications are found on nucleosomal histone proteins that package DNA and can be captured by ChIP-seq methods. ATAC-seq identifies areas of open chromatin which are enriched in active enhancers and can be combined with chromosome conformation capture (3C) approaches to generate information about promoter/enhancer interactions within these regions. Finally, RNA-seq provides a means to measure the transcriptional output of these complex interactions.

molecular level and potentially opens new avenues for innovative therapeutic interventions.

More recently, a potential role for snoRNA in SCZ has emerged, particularly in the anterior cingulate cortex (ACC) (Ragan et al., 2017c; Smalheiser et al., 2014a), a brain region implicated in regulating a range of cognitive functions, such as empathy and emotion, that has been associated with several psychiatric disorders, including schizophrenia and depression. SnoRNAs, a subtype of ncRNAs, are recognized for their ability to regulate gene expression through chemical modifications to other ncRNAs (Huang et al., 2022; Wu et al., 2016). SnoRNA molecules typically mediate expression by methylation or pseudouridylation of target transfer RNA (tRNA) and ribosomal RNA (rRNA), processes which are interrupted in disease (Reichow et al., 2007).

RNA-seq analysis of small RNA species unveiled differential expression of snoRNA transcripts in SCZ, revealing sex-based differences both between males and females, and between cases and controls (Ragan et al., 2017). This indicates a sex-specific dysregulation occurring in specific brain regions among SCZ patients. Furthermore, a distinct class of snoRNAs exhibited substantial alterations in the synaptosomes of individuals with SCZ, contributing valuable insights into the intricacies of synaptic dysfunction, and loss, observed in SCZ patients (Smalheiser et al., 2014). This nuanced exploration of the role of snoRNAs in SCZ extends our understanding of the molecular mechanisms underpinning the disorder.

lncRNA influences chromatin structure and mRNA transcription within the nucleus (Wilusz et al., 2008). In the cytoplasm, their role extends to post-transcriptional modification of mRNA and post-translational modifications of proteins. Single-cell RNA-seq has unveiled distinct expression patterns of lncRNAs in both healthy and diseased brains (Barry et al., 2014a; Elkouris et al., 2019; Naghavi-Gargari et al., 2019). As critical regulators of neuronal-cell lineage and oligodendrocyte maturation, lncRNAs emerge as pivotal players in the exploration of neuropsychiatric disorders (Mercer et al., 2010). Studies have revealed altered levels of lncRNAs in the blood and brain of individuals with early-onset SCZ, suggesting their potential as both biomarkers and therapeutic targets (Lai et al., 2011; Ren et al., 2015). A comprehensive analysis of the role of lncRNAs in SCZ pathogenesis identified 250 differentially expressed lncRNAs in the amygdala between SCZ-affected individuals and controls (Liu et al., 2018). Notably, one such lncRNA maps to the neurogranin (NRGN) gene, an important coding region exhibiting significantly higher expression levels in SCZ patients. NRGN is integral to hippocampal and ACC function, through calcium signaling pathways, so its aberrant function in SCZ may contribute to the neurocognitive deficits associated with the disorder (Guo et al., 2022; Ni et al., 2021). Moreover, lncRNAs contribute to SCZ pathogenesis through their involvement in alternative splicing, wherein aberrant alternative splicing in specific SCZ risk loci (e.g., DISC1 and ErbB4) is linked to reduced neuronal function and impaired synapse development (Barry et al., 2014). This multifaceted role of lncRNAs in regulating diverse cellular processes underscores their significance in deciphering the intricate molecular underpinnings of SCZ.

2.5. Epigenetic regulation by DNA methylation.

mRNA alternative splicing is also regulated by DNA methylation (Shukla et al., 2011), another major component of epigenetic regulation. CREs, including promoter regions, have been found to be hypermethylated in SCZ genes in the frontal lobe, specifically in the prefrontal cortex (PFC) (Roussos et al., 2014). The PFC contributes to social behavior and personality development (Bahia et al., 2013) An example of such variation is Reelin (RELN), an important extracellular matrix-associated glycoprotein that is most abundant in GABAergic neurons (D'Arcangelo et al., 1997), and which has been shown to have depleted protein and mRNA levels of up to 50 % in post-mortem tissue of SCZ patients (Impagnatiello et al., 1998; Yin et al., 2020). The RELN gene promoter is hypermethylated at CpG islands, leading to reduced RELN gene expression, and, ultimately, Reelin protein synthesis (Eastwood and Harrison, 2006; Impagnatiello et al., 1998). Given that Reelin protein is an essential regulator of neuronal migration, positioning, and synaptic plasticity in complex brain development mechanisms, its dysregulation in SCZ further indicates that SCZ is associated with disruption of critical neuronal development mechanisms.

SOX10, also identified as a risk factor for SCZ, encodes an oligodendrocyte-specific transcription factor with critical implications in neurodevelopment and oligodendrocyte function (Sullivan et al., 2018). Dysregulation of SOX10 activity is associated with changes in DNA methylation at CpG islands, and reduced SOX10 expression has been correlated with hypermethylation (Chen et al., 2021). Disruption of SOX10 function, as observed in several knockout experiments, results in the absence of glia in the peripheral nervous system and reduced myelin production (Lai et al., 2021; Mertelmeyer et al., 2020). In the context of SCZ, disruption of myelin and oligodendrocyte activity is believed to contribute to cognitive symptoms by affecting synapse development and function (Takahashi et al., 2011). The study and understanding of risk genes, such as RELN and SOX10, provides valuable insights into the molecular mechanisms underlying complex disorders such as SCZ.

2.6. Histone epigenetic regulation

Methylation of Histone H3 Lysine 4 (H3K4) is associated with active gene expression, and its strict regulation plays a critical role in proper brain development (Pekowska et al., 2011). Indeed, it has been shown that hundreds of subject specific SCZ GWAS variants display differential H3K4 methylation. This has been observed using genome-wide histone methylation studies, involving the powerful chromatin immunoprecipitation sequencing (ChIP-seq) approach, in conjunction with RNA-seq, and next-generation sequencing (NGS) methods (Fig. 2) (Kano et al., 2013).

Another comparison of H3K4-trimethylation landscapes in neuronal and glial cells from early to late childhood showed significant remodeling of the H3K4 methylation profile in SCZ genes involved in oxidative stress, metabolism and synaptic signaling. Indeed, Shulha and colleagues showed that aberrant expression of these genes over time can contribute to SCZ pathology (Shulha et al., 2013). Furthermore, disruptions to the remodeling process during early childhood caused by genetic variation and environmental factors are linked to neurodevelopmental diseases, including autism spectrum disorder (ASD) and intellectual disability (Smith et al., 2010).

2.7. Glutamate hypothesis

The N-methyl-D-aspartate (NMDA) receptor is a glutamate receptor that plays a vital role in synaptic plasticity and cortical maturation (Morris et al., 1986). NMDA receptors are key mediators of calcium signaling at excitatory synapses, and the receptor subunit composition changes during neuronal development, synaptic activity, and sensory experiences, giving rise to synaptic plasticity (Zhong et al., 2006). Calcium influx through NMDA receptors is critical for neurotransmission, and disruptions to this channel impact neuronal function. NMDA receptor hyperfunction is implicated in several common neurodegenerative disorders, while NMDA receptor hypofunction is associated with disease progression and manifestation (Beck et al., 2020; Wang et al., 2020). Several major findings have led to the consensus that NMDA receptor hypofunction at the postsynaptic membrane of glutamate synapses is causally associated with cellular phenotypes of SCZ (Moghaddam and Javitt, 2012). Altered methylation in NMDA receptor subunit genes, GRIN2A and 2B, has been identified in SCZ (Gavin and Sharma, 2010; Myers et al., 2019). The GRIN gene family are important SCZ genes that have recently been shown (by eQTL association with GWAS enrichment data) to be differentially expressed in SCZ (Myers et al., 2019; Trubetskoy et al., 2022). Furthermore, PTVs discovered in

the GRIN genes from the SCHEMA study, mentioned previously, provide genetic support that glutamate signaling at the synapse is important for the pathophysiology of SCZ (Singh et al., 2022); a finding that is consistent with previous pharmacological studies. Other SCZ risk loci that affect glutamatergic transmission via their impact on SRR, GRM3, and GRIA1 expression are located in non-coding regions of the genome, providing further evidence of a functional link between 3D organization of the genome and non-coding SNPs (Fullard et al., 2017; International Schizophrenia Consortium et al., 2009).

NMDA receptor signaling *via* intracellular signal transduction pathways, such as the AKT-GSK3β signaling pathway, is modulated by several high-risk SCZ genes, including DISC1 and NRG1 (Roussos et al., 2012; Roussos and Haroutunian, 2014; Sekar et al., 2016). AKT signaling is a crucial signal transduction pathway that promotes cell survival and growth (Hu et al., 2015). Dysregulation of AKT signaling is directly related to some of the most common and incurable disorders in humans, including cancers, cardiovascular and neurological diseases, and supports a role for the NMDA receptor in the glutamate and synapse hypothesis of SCZ.

The Mitogen-Activated Protin Kinase (MAPK) signaling pathway is also mediated by glutamate binding at NMDA receptors. Activation of the MAPK pathway ultimately leads to the activation of Extracellular Signal-Regulated Kinase (ERK), a signaling molecule that modulates gene expression in various cellular processes such as synaptic plasticity, neuronal survival, and differentiation (Boggio et al., 2007). Dysregulated MAPK/ERK signaling through altered NMDA receptors could account for some of the phenotypic characteristics observed in SCZ. This abnormal activity was characterized in the ACC and the dorsolateral prefrontal cortex (DLPFC) by examining differential MAPK-associated protein profiles between SCZ cases and controls (Funk et al., 2012). Increased levels of Rack1, Fyn and Ckd5 in the DLPFC, and decreased expression of Rap2, JNK1 and JNK2 were observed in the ACC, further implicating this brain region in the etiology of SCZ.

These findings suggest that SCZ might result from alterations of signaling mediated by multiple neurotransmitters, affecting several neuroepigenetic processes, rather than via a single mechanism. Other hypotheses exist to explain the mechanisms underlying SCZ, like the dopamine hypothesis (outlined below), genetic factors, environmental stress, and inflammation, but it is likely that these hypotheses are not mutually exclusive of each other and that a combination of some or all of them might contribute to the disease.

2.8. Dopamine hypothesis

The Dopamine Hypothesis suggests that an imbalance of dopamine contributes to psychotic symptoms in SCZ (Carlsson and Lindqvist, 1963). It proposes that hyperactivity of dopamine transmission in certain brain regions contributes to positive SCZ symptoms. Postmortem studies reveal dopamine imbalance in SCZ patients (Purves-Tyson et al., 2017), and dopamine receptor blocker drugs have been reported to assist in controlling positive symptoms (Ceraso et al., 2020). Included among the genes associated with increased risk of SCZ, is the gene encoding the dopamine D2 receptor (DRD2). SNPs found at the DRD2 locus may dysregulate dopaminergic neurotransmission by altering the receptor's function (Edwards et al., 2016). Dopamine not only plays a role in dopaminergic pathways, but also has an indirect function in GABAergic neurons (Sano et al., 2013). Dopamine maintains essential homeostasis between the pathways to maintain normal neuronal function and deficits in SCZ can be explained in part by this hypothesis.

2.9. Measuring expression

2.9.1. RNA-seq.

RNA-seq has revolutionized the landscape of SCZ research, contributing significantly to our knowledge of the intricate interplay of genetic and epigenetic factors contributing to the disorder, as detailed in the previous sections. Gene expression analysis, i.e., measuring the level of gene transcription, has enabled us to understand the molecular impact of risk variants, including identification of the target gene of an affected CRE and identification of alternative splicing events (Merrick et al., 2013; Worsley-Hunt et al., 2011). RNA-seq is performed on DNA sequencing platforms by reverse transcribing RNA molecules to double stranded complementary DNA (cDNA) molecules.

While procuring access to fresh human brain specimens can be challenging (Griffin et al., 2022), several brain banks exist with extensive archives of clinically interesting brain specimens including the VA Biorepository Brain Bank, the UK Brain Bank, and Rush Alzheimer's Disease Center. Generally, banks fix one hemisphere for immunohistochemistry experiments, while the other hemisphere is frozen for molecular analysis (McFadden et al., 2019). Upon thawing, the cell membrane is lost and, with it, the RNA content of the cytoplasm. When working with frozen material, researchers are therefore restricted to working with nuclei. Single-nuclei RNA-seq (snRNA-seq) has been successfully performed in frozen tissue and involves gentle dissociation of the tissue to facilitate isolation of nuclei (Jiang et al., 2023). Isolated cells/nuclei are processed using downstream assays, e.g., ATAC-seq, or single-cell/nuclei partitioning approaches (e.g., using the 10x Genomics Chromium platform).

2.9.2. ATAC-seq and Hi-C

The development of high-throughput next generation sequencing (NGS) methods has enabled researchers to move towards characterizing the epigenetic landscape of diseases in order to provide a deeper understanding of disease pathology (Costa et al., 2013; Zhang et al., 2014). Such assays include ATAC-seq, ChIP-seq and DNase I hypersensitive sites (Dnase1) sequencing (Fig. 2) (Buenrostro et al., 2013, 2015; Raha et al., 2010; Song and Crawford, 2010).

ATAC-seq is a sequencing method that identifies open chromatin regions (OCRs) and can be performed on bulk tissue, or at the level of individual cells (Buenrostro et al., 2015; Zhu et al., 2022). Functionally active CREs are located in OCRs and different cell-types have characteristic patterns of open chromatin, reflecting their functional diversity (Fullard et al., 2018; Hauberg et al., 2020). In addition, using a technique called Transcription Factor (TF) Footprinting, ATAC-seq can also provide useful information regarding TF occupancy at enhancers (Bentsen et al., 2020; Fullard et al., 2017). The ATAC-seq method uses a genetically engineered bacterial enzyme Tn5, a highly active transposase that inserts primers to facilitate enrichment prior to high-throughput sequencing. Tn5 recognizes and binds to OCRs by targeting nucleosome-free DNA and linker DNA between nucleosomes (Sato et al., 2019). Tn5 cleaves the target DNA and inserts short sequencing adaptors into the open chromatin sites, in a process known as tagmentation (Buenrostro et al., 2013).

Analysis of transcriptionally active OCRs revealed enrichment of SCZ variants in the accessible chromatin regions of the prefrontal cortex from 135 individuals with SCZ, compared to controls (Bryois et al., 2018). This dataset showed that SCZ variants play a role in regulating chromatin accessibility in disease. Similarly, Hoffman and colleagues (2019) analyzed ATAC-seq data from cells of the DLPFC of 269 individuals and identified SCZ risk-alleles within OCRs. Substantial differences in chromatin structure were found between glutamatergic neurons, GABAergic neurons, and microglia; indicative of cell-type specific variation in chromatin accessibility. Glutamatergic neurons, in particular, were enriched for SCZ variants; an observation that further supports the hypothesis that glutamate neurotransmitter deficiency is a likely contributor to the disease pathology (Hu et al., 2015). These results indicate that ATAC-seq is a useful tool (at both bulk and single-cell level) for obtaining chromatin accessibility of genome-wide significance across brain regions and cell types and for fine mapping causative risk variants.

Further mapping of the epigenetic landscape can be achieved by

combining data from multiple, complementary, approaches (PsychENCODE Consortium et al., 2015). As part of an ongoing effort to characterize gene regulatory networks in the human brain, the PsychENCODE study has successfully integrated interactome (Hi-C), chromatin accessibility (ATAC-seq) and transcriptomic datasets (RNA-seq) from diseased cohorts, to link active promoters and enhancers to SCZ genes and to generate a reference map of regulatory networks (Fig. 2). PsychENCODE identified 142 SCZ GWAS risk loci linked to disease genes governing fetal development and glutamatergic neuron signaling (Girdhar et al., 2022).

Chromosome Conformation Capture (3C)-based methods, including Hi-C, can be used to infer direct interactions between genomic loci (e.g., enhancers and their target promoter) in 3-D space (Lu et al., 2020). Coupled with other approaches, including RNA-seq, ChIP-seq and ATAC-seq, these approaches provide a powerful means to interrogate the gene expression regulatory landscape at genome wide resolution (Fulco et al., 2019; Schoenfelder et al., 2015). Hi-C detects chromatin interactions at high resolution in the nucleus by cross-linking cells with formaldehyde, chromosome isolation, restriction enzyme digestion and re-ligation, and sequencing of the cross-linked DNA fragments (Mifsud et al., 2015). CREs do not necessarily regulate the function of the nearest gene along the linear genome and can be brought into functional contact with their gene target through looping of intervening genomic DNA (Oudelaar and Higgs, 2021).

In SCZ, the epigenetic landscape changes dramatically over time in a brain-region and cell-type specific manner, as identified by scATAC-seq developmental analysis on cultured cerebral organoids (Ziffra et al., 2021). This dynamic reorganization of the 3D structure of chromatin was further characterized by Hi-C, leading to the identification of many non-proximal SCZ SNPs that interact with important genes involved in brain development pathways (Won et al., 2016). A strong SCZ association in hypomethylated regions was identified in the DLPFC in the first five years of development (Jaffe et al., 2015). Formation of synaptic connections occurs in this early development stage, further supporting an SCZ association with abnormal synapse formation. Thus, chromatin interactome characterization is important in SCZ as it facilitates the direct observation of CRE/gene interactions, allowing for the identification of affected molecular pathways and potential druggable targets. While Hi-C is compatible with NGS platforms, and can be used to analyze the 3D genome at unprecedented resolution (Beagan et al., 2016; Schoenfelder et al., 2015), it is both experimentally and computationally challenging, limiting its current practicality in terms of scalability and robustness (Lu et al., 2020).

2.9.3. Multi-omic ATAC and RNA-seq

ATAC-seq is especially powerful when used in conjunction with RNA-seq for multi-omic studies (Hauberg et al., 2020). Simultaneous transcriptomic and epigenomic analyses enables mapping of *cis*-acting regulatory elements onto OCRs, to provide a complete picture of gene regulatory networks that are disrupted in disease in specific subpopulations (Wang et al., 2020; Zhang et al., 2022). Combining the ATAC and gene expression steps into a single assay increases the accuracy of the results by eliminating variability that may occur from performing two separate assays in independent populations of cells/nuclei (Zhang et al., 2022). The single-cell ATAC and gene expression multi-omic assay is a novel technique released by 10X Genomics in 2020, and as such has yet to be extensively critiqued in the literature. However, as shown by Ma et al. (2022), it represents a promising method for delineating neuronal cell type transcriptional and regulatory heterogeneity; enabling the identification of new cell subtype specific CREs in the DLPFC. Moreover, Adams et al. (2022) performed paired snRNA-seq and snATAC-seq on 31 case-controlled individuals to study genetic contributions to Parkinson's Disease (PD) and were able to identify a previously undiscovered disease-associated oligodendrocyte subtype. Single-nuclei multi-omic analysis of aliquots of frozen human brain specimens across six developmental time points (including two fetal points and, postnatally, ranging from 0 to 39 years old) identified gene expression modules that regulate cell-fate choice in the developing human cortex (Zhu et al., 2022). The outcomes of these preliminary multi-omic studies demonstrate the utility of this approach in studying psychiatric disorders, and its potential application in the study of epigenetic regulation in different types of neuronal cells.

2.10. Future directions

While this review details our current understanding of the (epi)genetics of SCZ risk, much less is known about the contribution of the identified variants. Thus, the next grand challenge is the functional assessment of SCZ risk variants in model systems.

A number of animal models of SCZ have been developed (Lee and Zhou, 2019; White and Siegel, 2016), with the potential to facilitate candidate drug testing. SCZ CNVs modelled in mice, for example, resulted in the presentation of some of the behavioral and electrophysiological characteristics of SCZ (Forsingdal et al., 2019). Recapitulating the high level of SCZ-associated genetic variation in SCZ animal models, however, remains a major challenge and animal models have, as of yet, failed to fully reflect the true nature of the disease in humans (Białoń and Wąsik, 2022; White and Siegel, 2016). This is compounded by the fact that rodent models do not exhibit higher mental functions, making modelling mental illnesses, as a whole, a difficult prospect in model organisms (Nestler and Hyman, 2010). The inherent differences between human and rodent brains additionally raises questions about the reliability and applicability of the results (Vesterinen et al., 2010).

In an attempt to mitigate these issues, the use of model human cell lines has increased. Created from differentiation of patient-derived induced pluripotent stem cells (iPSCs) into neuronal cells, glia, and brain organoids, these cell lines could potentially help to elucidate the effects of non-coding SNPS on neurodevelopment; giving rise to new insights into the disease (Kampmann, 2020; Noh et al., 2017). However, reliable differentiation of iPSCs into neuronal progenitor cells remains technically challenging, and currently requires significant further development to achieve reliable disease modelling results (Fernando-pulle et al., 2018).

Another approach involves the generation of brain organoids; 3D tissue models generated from iPSCs (Choi et al., 2022; Qian et al., 2018). Cerebral organoid disease models generated from iPSCs from SCZ-affected individuals have recapitulated important features of neurodevelopment, including disrupted neurogenesis and lower neuron numbers by proteomic analysis (Notaras et al., 2021). Despite their potential in modeling neurodevelopmental disorders, brain organoids also present some significant disadvantages. One of the main drawbacks is their limited complexity when compared to real brains. While they can simulate certain aspects of neural development and function, brain organoids lack the full diversity and structural intricacies of the human brain (Qian et al., 2017, 2018). This might restrict the accuracy and translatability of the findings obtained from these models, potentially hindering the development of effective therapeutic interventions for neurological conditions like SCZ.

Additionally, ethical considerations permeate the use of brain organoids derived from human cells, demanding meticulous scrutiny, particularly in the context of human dignity. A pressing concern revolves around the potential manifestation of consciousness and the prospect of suffering within these miniature cerebral models, blurring the lines between scientific exploration and ethical thresholds (Hyun et al., 2020). A further ethical issue arises from the origin of the cells required for generating organoids, involving human embryonic stem cells. There are legitimate concerns regarding the sanctity of life and the ethical treatment of biological materials (Boers and Bredenoord, 2018). The responsible and ethical use of such sources is imperative and can be achieved through correct biomaterials procurement and donor consent procedures (Salles et al., 2019). By addressing these concerns, the scientific community can further the frontier of knowledge while

upholding the intrinsic dignity of life.

Advances in genome editing, and related techniques, have nonetheless resulted in some recent significant breakthroughs in the functional assessment of SCZ risk variants (Avramopoulos, 2018; Michael Deans and Brennand, 2021). CRISPR-based methods, in particular, have been applied to experimental disease models by deleting or inserting SCZ risk variants, through CRISPR interference (CRISPRi) or CRISPR activation (CRISPRa), to better understand their contribution to the disease pathogenesis (Tian et al., 2019; Townsley et al., 2022). Furthermore, a relatively new genomics tool known as Expanded CRISPR-compatible Cellular Indexing of Transcriptomes and Epitopes by sequencing (ECCITE-seq), developed at the New York Genome Center by Mimitou and coworkers, (2019), enables multiplexed detection of proteomes, transcriptomes, and CRISPR guide-RNAs, at single-cell resolution. The detection of CRISPR perturbations with multimodal readouts represents a powerful advancement that contributes to the robustness and efficiency of single-cell CRISPR screening methods (Mimitou et al., 2019). The integration of CRISPR-genome editing and ECCITE-seq not only represents an important strategy for demonstrating the cell-type specific effects of SCZ-associated variants, but, importantly, facilitates the development of biomarkers for improved diagnosis, as well as potential novel therapeutic strategies.

3. Conclusion

In conclusion, this review navigates the complex landscape of the genetics of SCZ, encompassing its genetic foundations, contributions of epigenetic factors, and the regulatory roles of specific epigenetic mechanisms. The transformative impact of single-cell analysis emerges as an indispensable technology, offering nuanced insights into the heterogeneity of cellular responses. However, as we stand at the forefront of SCZ research, looking beyond the genome, the next grand challenge will, undoubtably, be unravelling the functional effects of SCZ variation through disease modelling. The future is bright, the future is functional.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

Adams, L., Kyung Song, M., Tanaka, Y., Kim, Y., Kim, Y.-S., 2022. Single-nuclei paired multiomic analysis of young, aged, and Parkinson's disease human midbrain reveals age-associated glial changes and their contribution to Parkinson's disease. MedRxiv.

Aicher, T. P., Carroll, S., Raddi, G., Gierahn, T., Wadsworth, M. H., Hughes, T. K., Love, C., and Shalek, A. K. (2019). Seq-Well: A Sample-Efficient, Portable Picowell Platform for Massively Parallel Single-Cell RNA Sequencing. *Methods in Molecular Biology (Clifton, N.J.)*, *1979*, 111–132. 10.1007/978-1-4939-9240-9_8.

Akbarian, S., 2014. Epigenetic mechanisms in schizophrenia. Dialogues Clin. Neurosci. 16 (3), 405–417.

Alkaslasi, M.R., Piccus, Z.E., Hareendran, S., Silberberg, H., Chen, L., Zhang, Y., Petros, T.J., Le Pichon, C.E., 2021. Single nucleus RNA-sequencing defines unexpected diversity of cholinergic neuron types in the adult mouse spinal cord. Nat. Commun. 12 (1), 2471. https://doi.org/10.1038/s41467-021-22691-2.

American Psychiatric Association. (2013). Diagnostic and Statistical Mental Disorders (Dsm 5). In *American Psychiatric Association*.

Andrews, T.S., Kiselev, V.Y., McCarthy, D., Hemberg, M., 2021. Tutorial: guidelines for the computational analysis of single-cell RNA sequencing data. Nat. Protoc. 16 (1), 1–9. https://doi.org/10.1038/s41596-020-00409-w.

Angerer, P., Simon, L., Tritschler, S., Wolf, F.A., Fischer, D., Theis, F.J., 2017. Single cells make big data: New challenges and opportunities in transcriptomics. Curr. Opin. Syst. Biol. 4, 85–91. https://doi.org/10.1016/j.coisb.2017.07.004.

Avramopoulos, D., 2018. Recent Advances in the Genetics of Schizophrenia. Mol. Neuropsych. 4 (1), 35–51. https://doi.org/10.1159/000488679.

Bahia, V.S., Takada, L.T., Caixeta, L., Lucato, L.T., Porto, C.S., Nitrini, R., 2013. Prefrontal damage in childhood and changes in the development of personality: a case report. Dement. Neuropsycholo. 7 (1), 132–135. https://doi.org/10.1590/S1980-57642013DN70100019.

Barry, G., Briggs, J.A., Vanichkina, D.P., Poth, E.M., Beveridge, N.J., Ratnu, V.S., Nayler, S.P., Nones, K., Hu, J., Bredy, T.W., Nakagawa, S., Rigo, F., Taft, R.J., Cairns, M.J., Blackshaw, S., Wolvetang, E.J., Mattick, J.S., 2014. The long non-coding RNA Gomafu is acutely regulated in response to neuronal activation and involved in schizophrenia-associated alternative splicing. Mol. Psychiatry 19 (4), 486–494. https://doi.org/10.1038/mp.2013.45.

Batiuk, M.Y., Martirosyan, A., Wahis, J., de Vin, F., Marneffe, C., Kusserow, C., Koeppen, J., Viana, J.F., Oliveira, J.F., Voet, T., Ponting, C.P., Belgard, T.G., Holt, M. G., 2020. Identification of region-specific astrocyte subtypes at single cell resolution. Nat. Commun. 11 (1), 1220. https://doi.org/10.1038/s41467-019-14198-8.

Beagan, J.A., Gilgenast, T.G., Kim, J., Plona, Z., Norton, H.K., Hu, G., Hsu, S.C., Shields, E.J., Lyu, X., Apostolou, E., Hochedlinger, K., Corces, V.G., Dekker, J., Phillips-Cremins, J.E., 2016. Local Genome Topology Can Exhibit an Incompletely Rewired 3D-Folding State during Somatic Cell Reprogramming. Cell Stem Cell 18 (5), 611–624. https://doi.org/10.1016/j.stem.2016.04.004.

Beck, K., Hindley, G., Borgan, F., Ginestet, C., McCutcheon, R., Brugger, S., Driesen, N., Ranganathan, M., D'Souza, D.C., Taylor, M., Krystal, J.H., Howes, O.D., 2020. Association of Ketamine With Psychiatric Symptoms and Implications for Its Therapeutic Use and for Understanding Schizophrenia. JAMA Netw. Open 3 (5), e204693.

Bentsen, M., Goymann, P., Schultheis, H., Klee, K., Petrova, A., Wiegandt, R., Fust, A., Preussner, J., Kuenne, C., Braun, T., Kim, J., Looso, M., 2020. ATAC-seq footprinting unravels kinetics of transcription factor binding during zygotic genome activation. Nat. Commun. 11 (1), 4267. https://doi.org/10.1038/s41467-020-18035-1.

Bernstein, H.-G., Steiner, J., Guest, P.C., Dobrowolny, H., Bogerts, B., 2015. Glial cells as key players in schizophrenia pathology: recent insights and concepts of therapy. Schizophr. Res. 161 (1), 4–18. https://doi.org/10.1016/j.schres.2014.03.035.

Białoń, M., Wąsik, A., 2022. Advantages and Limitations of Animal Schizophrenia Models. Int. J. Mol. Sci. 23 (11), 5968. https://doi.org/10.3390/ijms23115968.

Boers, S.N., Bredenoord, A.L., 2018. Consent for governance in the ethical use of organoids. Nat. Cell Biol. 20 (6), 642–645. https://doi.org/10.1038/s41556-018-0112-5.

Boggio, E.M., Putignano, E., Sassoè-Pognetto, M., Pizzorusso, T., Giustetto, M., Mansvelder, H., 2007. Visual Stimulation Activates ERK in Synaptic and Somatic Compartments of Rat Cortical Neurons with Parallel Kinetics. PLoS One 2 (7), e604.

Bond, A.M., Vangompel, M.J.W., Sametsky, E.A., Clark, M.F., Savage, J.C., Disterhoft, J. F., Kohtz, J.D., 2009. Balanced gene regulation by an embryonic brain ncRNA is critical for adult hippocampal GABA circuitry. Nat. Neurosci. 12 (8), 1020–1027. https://doi.org/10.1038/nn.2371.

Bryois, J., Garrett, M.E., Song, L., Safi, A., Giusti-Rodriguez, P., Johnson, G.D., Shieh, A. W., Buil, A., Fullard, J.F., Roussos, P., Sklar, P., Akbarian, S., Haroutunian, V., Stockmeier, C.A., Wray, G.A., White, K.P., Liu, C., Reddy, T.E., Ashley-Koch, A., Sullivan, P.F., Crawford, G.E., 2018. Evaluation of chromatin accessibility in prefrontal cortex of individuals with schizophrenia. *Nature*. Communications 9 (1). https://doi.org/10.1038/s41467-018-05379-y.

Buenrostro, J.D., Giresi, P.G., Zaba, L.C., Chang, H.Y., Greenleaf, W.J., 2013. Transposition of native chromatin for fast and sensitive epigenomic profiling of open chromatin, DNA-binding proteins and nucleosome position. Nat. Methods 10 (12), 1213–1218.

Buenrostro, J.D., Wu, B., Chang, H.Y., Greenleaf, W.J., 2015. ATAC-seq: A method for assaying chromatin accessibility genome-wide. Curr. Protoc. Mol. Biol. 2015 https://doi.org/10.1002/0471142727.mb2129s109.

Carlsson, A., Lindqvist, M., 1963. Effect of Chlorpromazine or Haloperidol on Formation of 3-Methoxytyramine and Normetanephrine in Mouse Brain. Acta Pharmacol. Toxicol. 20 (2), 140–144. https://doi.org/10.1111/j.1600-0773.1963.tb01730.x.

Ceraso, A., LIN, J. J., Schneider-Thoma, J., Siafis, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Davis, J. M., & Leucht, S. (2020). Maintenance treatment with antipsychotic drugs for schizophrenia. *Cochrane Database of Systematic Reviews*, *2020* (8). 10.1002/14651858.CD008016.pub3.

Chambers, D.C., Carew, A.M., Lukowski, S.W., Powell, J.E., 2019. Transcriptomics and single-cell RNA-sequencing. Respirology (Carlton Vic.) 24 (1), 29–36. https://doi.org/10.1111/resp.13412.

Charlson, F.J., Ferrari, A.J., Santomauro, D.F., Diminic, S., Stockings, E., Scott, J.G., McGrath, J.J., Whiteford, H.A., 2018. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. Schizophr. Bull. 44 (6), 1195–1203. https://doi.org/10.1093/schbul/sby058.

Chen, X., Huang, N.-X., Cheng, Y.-J., Cai, Q.-Y., Tian, Y.-P., Chen, X.-S., Xiao, L., 2021. DNA Hypermethylation Induced by L-Methionine Leads to Oligodendroglial and Myelin Deficits and Schizophrenia-Like Behaviors in Adolescent Mice. Front. Neurosci. 15, 659853 https://doi.org/10.3389/fnins.2021.659853.

Chen, S., Sun, X., Niu, W., Kong, L., He, M., Li, W., Zhong, A., Lu, J., Zhang, L., 2016. Aberrant Expression of Long Non-Coding RNAs in Schizophrenia Patients. Med. Sci. Monit. 22, 3340–3351. https://doi.org/10.12659/MSM.896927.

Choi, N.Y., Lee, M.-Y., Jeong, S., 2022. Recent Advances in 3D-Cultured Brain Tissue Models Derived from Human iPSCs. BioChip J. 16 (3), 246–254. https://doi.org/10.1007/s13206-022-00075-y.

Cohen, S.M., Tsien, R.W., Goff, D.C., Halassa, M.M., 2015. The impact of NMDA receptor hypofunction on GABAergic neurons in the pathophysiology of schizophrenia. Schizophr. Res. 167 (1–3), 98–107. https://doi.org/10.1016/j.schres.2014.12.026.

Colman-Lerner, A., Gordon, A., Serra, E., Chin, T., Resnekov, O., Endy, D., Gustavo Pesce, C., Brent, R., 2005. Regulated cell-to-cell variation in a cell-fate decision system. Nature 437 (7059), 699–706.

Costa, V., Aprile, M., Esposito, R., Ciccodicola, A., 2013. RNA-Seq and human complex diseases: recent accomplishments and future perspectives. Eur. J. Hum. Genet. 21 (2), 134–142. https://doi.org/10.1038/ejhg.2012.129.

D'Arcangelo, G., Nakajima, K., Miyata, T., Ogawa, M., Mikoshiba, K., Curran, T., 1997. Reelin is a secreted glycoprotein recognized by the CR-50 monoclonal antibody. J. Neurosci. 17 (1), 23–31.

das Neves, R.P., Jones, N.S., Andreu, L., Gupta, R., Enver, T., Iborra, F.J., Weissman, J.S., 2010. Connecting variability in global transcription rate to mitochondrial variability. PLoS Biol. 8 (12) https://doi.org/10.1371/journal.pbio.1000560.

Dave, R.S., Khalili, K., 2010. Morphine treatment of human monocyte-derived macrophages induces differential miRNA and protein expression: impact on inflammation and oxidative stress in the central nervous system. J. Cell. Biochem. 110 (4), 834–845. https://doi.org/10.1002/jcb.22592.

Ding, J., Adiconis, X., Simmons, S.K., Kowalczyk, M.S., Hession, C.C., Marjanovic, N.D., Hughes, T.K., Wadsworth, M.H., Burks, T., Nguyen, L.T., Kwon, J.Y.H., Barak, B., Ge, W., Kedaigle, A.J., Carroll, S., Li, S., Hacohen, N., Rozenblatt-Rosen, O., Shalek, A.K., Villani, A.-C., Regev, A., Levin, J.Z., 2020. Systematic comparison of single-cell and single-nucleus RNA-sequencing methods. Nat. Biotechnol. 38 (6), 737–746.

Dixon, J.R., Selvaraj, S., Yue, F., Kim, A., Li, Y., Shen, Y., Hu, M., Liu, J.S., Ren, B., 2012. Topological domains in mammalian genomes identified by analysis of chromatin interactions. Nature 485 (7398), 376–380. https://doi.org/10.1038/nature11082.

Dobbyn, A., Huckins, L.M., Boocock, J., Sloofman, L.G., Glicksberg, B.S., Giambartolomei, C., Hoffman, G.E., Perumal, T.M., Girdhar, K., Jiang, Y., Raj, T., Ruderfer, D.M., Kramer, R.S., Pinto, D., Akbarian, S., Roussos, P., Domenici, E., Devlin, B., Sklar, P., Stahl, E.A., Sieberts, S.K., Sklar, P., Buxbaum, J., Devlin, B., Lewis, D., Gur, R., Hahn, C.-G., Hirai, K., Toyoshiba, H., Domenici, E., Essioux, L., Mangravite, L., Peters, M., Lehner, T., Lipska, B., Cicek, A.E., Lu, C., Roeder, K., Xie, L.u., Talbot, K., Hemby, S.E., Essioux, L., Browne, A., Chess, A., Topol, A., Charney, A., Dobbyn, A., Readhead, B., Zhang, B., Pinto, D., Bennett, D.A., Kavanagh, D.H., Ruderfer, D.M., Stahl, E.A., Schadt, E.E., Hoffman, G.E., Shah, H.R., Zhu, J., Johnson, J.S., Fullard, J.F., Dudley, J.T., Girdhar, K., Brennand, K.J., Sloofman, L.G., Huckins, L.M., Fromer, M., Mahajan, M.C., Roussos, P., Akbarian, S., Purcell, S.M., Hamamsy, T., Raj, T., Haroutunian, V., Wang, Y.-C., Gümüş, Z.H., Senthil, G., Kramer, R., Logsdon, B.A., Derry, J.M.J., Dang, K.K., Sieberts, S.K., Perumal, T.M., Visintainer, R., Shinobu, L.A., Sullivan, P.F., Klei, L.L., 2018. Landscape of Conditional eQTL in Dorsolateral Prefrontal Cortex and Co-localization with Schizophrenia GWAS. Am. J. Hum. Genet. 102 (6), 1169–1184.

Domingues, H.S., Portugal, C.C., Socodato, R., Relvas, J.B., 2016. Oligodendrocyte, Astrocyte, and Microglia Crosstalk in Myelin Development, Damage, and Repair. Front. Cell Dev. Biol. 4, 71. https://doi.org/10.3389/fcell.2016.00071.

Dong, P., Bendl, J., Misir, R., Shao, Z., Edelstien, J., Davis, D. A., Haroutunian, V., Scott, W. K., Acker, S., Lawless, N., Hoffman, G. E., Fullard, J. F., & Roussos, P. (2022). *Transcriptome and chromatin accessibility landscapes across 25 distinct human brain regions expand the susceptibility gene set for neuropsychiatric disorders* . doi: 10.1101/2022.09.02.506419.

Eastwood, S.L., Harrison, P.J., 2006. Cellular basis of reduced cortical reelin expression in schizophrenia. Am. J. Psychiatry 163 (3), 540–542.

Edwards, A.C., Bacanu, S.-A., Bigdeli, T.B., Moscati, A., Kendler, K.S., 2016. Evaluating the dopamine hypothesis of schizophrenia in a large-scale genome-wide association study. Schizophr. Res. 176 (2–3), 136–140. https://doi.org/10.1016/j.schres.2016.06.016.

Elkouris, M., Kouroupi, G., Vourvoukelis, A., Papagiannakis, N., Kaltezioti, V., Matsas, R., Stefanis, L., Xilouri, M., Politis, P.K., 2019. Long Non-coding RNAs Associated With Neurodegeneration-Linked Genes Are Reduced in Parkinson's Disease Patients. Front. Cell. Neurosci. 13, 58. https://doi.org/10.3389/fncel.2019.00058.

Fazel, S., Langström, N., Hjern, A., Grann, M., Lichtenstein, P., 2009. Schizophrenia, substance abuse, and violent crime. JAMA 301 (19). https://doi.org/10.1001/jama.2009.675.

Felling, R.J., Song, H., 2015. Epigenetic mechanisms of neuroplasticity and the implications for stroke recovery. Exp. Neurol. 268, 37–45. https://doi.org/10.1016/j.expneurol.2014.09.017.

Felling, R.J., Guo, J.U., Song, H., 2012. Neuronal activation and insight into the plasticity of DNA methylation. Epigenomics 4 (2), 125–127. https://doi.org/10.2217/epi.12.2.

Fernandopulle, M.S., Prestil, R., Grunseich, C., Wang, C., Gan, L., Ward, M.E., 2018. Transcription Factor-Mediated Differentiation of Human iPSCs into Neurons. Curr. Protoc. Cell Biol. 79 (1), e51.

Fleischman, A., Werbeloff, N., Yoffe, R., Davidson, M., Weiser, M., 2014. Schizophrenia and violent crime: a population-based study. Psychol. Med. 44 (14), 3051–3057.

Forsingdal, A., Jørgensen, T. N., Olsen, L., Werge, T., Didriksen, M., & Nielsen, J. (2019). Can Animal Models of Copy Number Variants That Predispose to Schizophrenia Elucidate Underlying Biology? In *Biological Psychiatry* (Vol. 85, Issue 1). 10.1016/j.biopsych.2018.07.004.

Fulco, C.P., Nasser, J., Jones, T.R., Munson, G., Bergman, D.T., Subramanian, V., Grossman, S.R., Anyoha, R., Doughty, B.R., Patwardhan, T.A., Nguyen, T.H., Kane, M., Perez, E.M., Durand, N.C., Lareau, C.A., Stamenova, E.K., Aiden, E.L., Lander, E.S., Engreitz, J.M., 2019. Activity-by-contact model of enhancer–promoter regulation from thousands of CRISPR perturbations. Nat. Genet. 51 (12), 1664–1669. https://doi.org/10.1038/s41588-019-0538-0.

Fullard, J.F., Giambartolomei, C., Hauberg, M.E., Xu, K., Voloudakis, G., Shao, Z., Bare, C., Dudley, J.T., Mattheisen, M., Robakis, N.K., Haroutunian, V., Roussos, P., 2017. Open chromatin profiling of human postmortem brain infers functional roles for non-coding schizophrenia loci. Hum. Mol. Genet. 26 (10), 1942–1951. https://doi.org/10.1093/hmg/ddx103.

Fullard, J.F., Hauberg, M.E., Bendl, J., Egervari, G., Cirnaru, M.-D., Reach, S.M., Motl, J., Ehrlich, M.E., Hurd, Y.L., Roussos, P., 2018. An atlas of chromatin accessibility in the adult human brain. Genome Res. 28 (8), 1243–1252. https://doi.org/10.1101/gr.232488.117.

Funk, A.J., McCullumsmith, R.E., Haroutunian, V., Meador-Woodruff, J.H., 2012. Abnormal Activity of the MAPK- and cAMP-Associated Signaling Pathways in Frontal Cortical Areas in Postmortem Brain in Schizophrenia. Neuropsychopharmacology 37 (4), 896–905. https://doi.org/10.1038/npp.2011.267.

Gavin, D.P., Sharma, R.P., 2010. Histone modifications, DNA methylation, and Schizophrenia. Neurosci. Biobehav. Rev. 34 (6), 882–888.

Gierahn, T.M., Wadsworth, M.H., Hughes, T.K., Bryson, B.D., Butler, A., Satija, R., Fortune, S., Love, J.C., Shalek, A.K., 2017. Seq-Well: portable, low-cost RNA sequencing of single cells at high throughput. Nat. Methods 14 (4), 395–398. https://doi.org/10.1038/nmeth.4179.

Girdhar, K., Hoffman, G.E., Bendl, J., Rahman, S., Dong, P., Liao, W., Hauberg, M.E., Sloofman, L., Brown, L., Devillers, O., Kassim, B.S., Wiseman, J.R., Park, R., Zharovsky, E., Jacobov, R., Flatow, E., Kozlenkov, A., Gilgenast, T., Johnson, J.S., Couto, L., Peters, M.A., Phillips-Cremins, J.E., Hahn, C.-G., Gur, R.E., Tamminga, C. A., Lewis, D.A., Haroutunian, V., Dracheva, S., Lipska, B.K., Marenco, S., Kundakovic, M., Fullard, J.F., Jiang, Y., Roussos, P., Akbarian, S., 2022. Chromatin domain alterations linked to 3D genome organization in a large cohort of schizophrenia and bipolar disorder brains. Nat. Neurosci. 25 (4), 474–483.

Gober, R., Ardalan, M., Shiadeh, S.M.J., Duque, L., Garamszegi, S.P., Ascona, M., Barreda, A., Sun, X., Mallard, C., Vontell, R.T., 2022. Microglia activation in postmortem brains with schizophrenia demonstrates distinct morphological changes between brain regions. Brain Pathol. 32 (1) https://doi.org/10.1111/bpa.13003.

Griffin, C.P., Paul, C.L., Alexander, K.L., Walker, M.M., Hondermarck, H., Lynam, J., 2022. Postmortem brain donations vs premortem surgical resections for glioblastoma research: viewing the matter as a whole. Neuro-Oncol. Adv. 4 (1) https://doi.org/10.1093/noajnl/vdab168.

Guo, B., Jiang, T., Wu, F., Ni, H., Ye, J., Wu, X., Ni, C., Jiang, M., Ye, L., Li, Z., Zheng, X., Li, S., Yang, Q., Wang, Z., Huang, X., Zhao, C., 2022. LncRNA RP5-998N21.4 promotes immune defense through upregulation of IFIT2 and IFIT3 in schizophrenia. Schizophrenia (heidelberg, Germany) 8 (1), 11. https://doi.org/10.1038/s41537-021-00195-8.

Gur, R.E., Gur, R.C., 2010. Functional magnetic resonance imaging in schizophrenia. Dialogues Clin. Neurosci. 12 (3), 333–343.

Harrison, P.J., Weinberger, D.R., 2005. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol. Psychiatry 10 (1), 40–68. https://doi.org/10.1038/sj.mp.4001558.

Hauberg, M.E., Creus-Muncunill, J., Bendl, J., Kozlenkov, A., Zeng, B., Corwin, C., Chowdhury, S., Kranz, H., Hurd, Y.L., Wegner, M., Børglum, A.D., Dracheva, S., Ehrlich, M.E., Fullard, J.F., Roussos, P., 2020. Common schizophrenia risk variants are enriched in open chromatin regions of human glutamatergic neurons. Nat. Commun. 11 (1), 5581. https://doi.org/10.1038/s41467-020-19319-2.

Hawrylycz, M.J., Lein, E.S., Guillozet-Bongaarts, A.L., Shen, E.H., Ng, L., Miller, J.A., van de Lagemaat, L.N., Smith, K.A., Ebbert, A., Riley, Z.L., Abajian, C., Beckmann, C.F., Bernard, A., Bertagnolli, D., Boe, A.F., Cartagena, P.M., Chakravarty, M.M., Chapin, M., Chong, J., Jones, A.R., 2012. An anatomically comprehensive atlas of the adult human brain transcriptome. Nature 489 (7416), 391–399. https://doi.org/10.1038/nature11405.

Henry, C.S., DeJongh, M., Best, A.A., Frybarger, P.M., Linsay, B., Stevens, R.L., 2010. High-throughput generation, optimization and analysis of genome-scale metabolic models. Nat. Biotechnol. 28 (9), 977–982. https://doi.org/10.1038/nbt.1672.

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T.M., Nordentoft, M., Glenthøj, B., 2018. Heritability of Schizophrenia and Schizophrenia Spectrum Based on the Nationwide Danish Twin Register. Biol. Psychiatry 83 (6), 492–498. https://doi.org/10.1016/j.biopsych.2017.08.017.

Hoffman, G.E., Bendl, J., Voloudakis, G., Montgomery, K.S., Sloofman, L., Wang, Y.-C., Shah, H.R., Hauberg, M.E., Johnson, J.S., Girdhar, K., Song, L., Fullard, J.F., Kramer, R., Hahn, C.-G., Gur, R., Marenco, S., Lipska, B.K., Lewis, D.A., Haroutunian, V., Hemby, S., Sullivan, P., Akbarian, S., Chess, A., Buxbaum, J.D., Crawford, G.E., Domenici, E., Devlin, B., Sieberts, S.K., Peters, M.A., Roussos, P., 2019. CommonMind Consortium provides transcriptomic and epigenomic data for Schizophrenia and Bipolar Disorder. Sci. Data 6 (1). https://doi.org/10.1038/s41597-019-0183-6.

Howes, O.D., Kapur, S., 2009. The dopamine hypothesis of schizophrenia: version III–the final common pathway. Schizophr. Bull. 35 (3), 549–562. https://doi.org/10.1093/schbul/sbp006.

Hu, W., MacDonald, M.L., Elswick, D.E., Sweet, R.A., 2015. The glutamate hypothesis of schizophrenia: evidence from human brain tissue studies. Ann. N. Y. Acad. Sci. 1338 (1), 38–57. https://doi.org/10.1111/nyas.12547.

Huang, Z., Du, Y., Wen, J., Lu, B., Zhao, Y., 2022. snoRNAs: functions and mechanisms in biological processes, and roles in tumor pathophysiology. Cell Death Discovery 8 (1), 259. https://doi.org/10.1038/s41420-022-01056-8.

Hyun, I., Scharf-Deering, J.C., Lunshof, J.E., 2020. Ethical issues related to brain organoid research. Brain Res. 1732, 146653 https://doi.org/10.1016/j.brainres.2020.146653.

Im, H.-I., Kenny, P.J., 2012. MicroRNAs in neuronal function and dysfunction. Trends Neurosci. 35 (5), 325–334. https://doi.org/10.1016/j.tins.2012.01.004.

Impagnatiello, F., Guidotti, A.R., Pesold, C., Dwivedi, Y., Caruncho, H., Pisu, M.G., Uzunov, D.P., Smalheiser, N.R., Davis, J.M., Pandey, G.N., Pappas, G.D., Tueting, P., Sharma, R.P., Costa, E., 1998. A decrease of reelin expression as a putative vulnerability factor in schizophrenia. Proc. Natl. Acad. Sci. 95 (26), 15718–15723. https://doi.org/10.1073/pnas.95.26.15718.

International Schizophrenia Consortium, Purcell, S.M., Wray, N.R., Stone, J.L., Visscher, P.M., O'Donovan, M.C., Sullivan, P.F., Sklar, P., 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460 (7256), 748–752. https://doi.org/10.1038/nature08185.

Jääskeläinen, E., Juola, P., Hirvonen, N., McGrath, J.J., Saha, S., Isohanni, M., Veijola, J., Miettunen, J., 2013. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr. Bull. 39 (6), 1296–1306. https://doi.org/10.1093/schbul/sbs130.

Jaffe, A.E., Gao, Y., Deep-Soboslay, A., Tao, R., Hyde, T.M., Weinberger, D.R., Kleinman, J.E., 2015. Mapping DNA methylation across development, genotype and schizophrenia in the human frontal cortex. Nat. Neurosci. 19 (1) https://doi.org/10.1038/nn.4181.

Jäkel, S., Dimou, L., 2017. Glial Cells and Their Function in the Adult Brain: A Journey through the History of Their Ablation. Front. Cell. Neurosci. 11, 24. https://doi.org/10.3389/fncel.2017.00024.

Javitt, D.C., 2009. When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. Annu. Rev. Clin. Psychol. 5, 249–275. https://doi.org/10.1146/annurev.clinpsy.032408.153502.

Jiang, A., Lehnert, K., Reid, S. J., Handley, R. R., Jacobsen, J. C., Rudiger, S. R., McLaughlan, C. J., Verma, P. J., Bawden, C. S., & Snell, R. G. (2023). *Isolated nuclei from frozen tissue are the superior source for single cell RNA-seq compared with whole cells*.

Kampmann, M., 2020. CRISPR-based functional genomics for neurological disease. In *Nature Reviews*. Neurology 16 (9), 465–480.

Kano, S., Colantuoni, C., Han, F., Zhou, Z., Yuan, Q., Wilson, A., Takayanagi, Y., Lee, Y., Rapoport, J., Eaton, W., Cascella, N., Ji, H., Goldman, D., Sawa, A., 2013. Genome-wide profiling of multiple histone methylations in olfactory cells: further implications for cellular susceptibility to oxidative stress in schizophrenia. Mol Psychiatry 18 (7), 740–742.

Karlsgodt, K.H., Sun, D., Cannon, T.D., 2010. Structural and functional brain abnormalities in schizophrenia. Curr. Dir. Psychol. Sci. 19 (4), 226–231.

Korn, J.M., Kuruvilla, F.G., McCarroll, S.A., Wysoker, A., Nemesh, J., Cawley, S., Hubbell, E., Veitch, J., Collins, P.J., Darvishi, K., Lee, C., Nizzari, M.M., Gabriel, S.B., Purcell, S., Daly, M.J., Altshuler, D., 2008. Integrated genotype calling and association analysis of SNPs, common copy number polymorphisms and rare CNVs. Nat. Genet. 40 (10), 1253–1260.

Kumar, S., Orlov, E., Gowda, P., Bose, C., Swerdlow, R.H., Lahiri, D.K., Reddy, P.H., 2022. Synaptosome microRNAs regulate synapse functions in Alzheimer's disease. NPJ Genom. Med. 7 (1), 47. https://doi.org/10.1038/s41525-022-00319-8.

Lai, X., Liu, J., Zou, Z., Wang, Y., Wang, Y., Liu, X., Huang, W., Ma, Y., Chen, Q., Li, F., Wu, G., Li, W., Wang, W., Yuan, Y., Jiang, B., 2021. SOX10 ablation severely impairs the generation of postmigratory neural crest from human pluripotent stem cells. Cell Death Dis. 12 (9), 814. https://doi.org/10.1038/s41419-021-04099-4.

Lai, C.-Y., Yu, S.-L., Hsieh, M.H., Chen, C.-H., Chen, H.-Y., Wen, C.-C., Huang, Y.-H., Hsiao, P.-C., Hsiao, C.K., Liu, C.-M., Yang, P.-C., Hwu, H.-G., Chen, W.J., Uddin, M., 2011. MicroRNA expression aberration as potential peripheral blood biomarkers for schizophrenia. PLoS One 6 (6), e21635.

Lee, G., Zhou, Y., 2019. NMDAR Hypofunction Animal Models of Schizophrenia. Front. Mol. Neurosci. 12, 185. https://doi.org/10.3389/fnmol.2019.00185.

Liu, Y., Chang, X., Hahn, C.-G., Gur, R.E., Sleiman, P.A.M., Hakonarson, H., 2018. Non-coding RNA dysregulation in the amygdala region of schizophrenia patients contributes to the pathogenesis of the disease. Transl. Psychiatry 8 (1), 44. https://doi.org/10.1038/s41398-017-0030-5.

Lu, L., Liu, X., Huang, W.-K., Giusti-Rodríguez, P., Cui, J., Zhang, S., Xu, W., Wen, Z., Ma, S., Rosen, J.D., Xu, Z., Bartels, C.F., Kawaguchi, R., Hu, M., Scacheri, P.C., Rong, Z., Li, Y., Sullivan, P.F., Song, H., Ming, G.-l., Li, Y., Jin, F., 2020. Robust Hi-C Maps of Enhancer-Promoter Interactions Reveal the Function of Non-coding Genome in Neural Development and Diseases. Mol. Cell 79 (3), 521–534.e15.

Luger, K., Mäder, A.W., Richmond, R.K., Sargent, D.F., Richmond, T.J., 1997. Crystal structure of the nucleosome core particle at 2.8 Å resolution. Nature 389 (6648), 251–260. https://doi.org/10.1038/38444.

Ma, S., Skarica, M., Li, Q., Xu, C., Risgaard, R.D., Tebbenkamp, A.T.N., Mato-Blanco, X., Kovner, R., Krsnik, Ž., de Martin, X., Luria, V., Martí-Pérez, X., Liang, D., Karger, A., Schmidt, D.K., Gomez-Sanchez, Z., Qi, C., Gobeske, K.T., Pochareddy, S., Sestan, N., 2022. Molecular and cellular evolution of the primate dorsolateral prefrontal cortex. Science 377 (6614). https://doi.org/10.1126/science.abo7257.

McFadden, W.C., Walsh, H., Richter, F., Soudant, C., Bryce, C.H., Hof, P.R., Fowkes, M., Crary, J.F., McKenzie, A.T., 2019. Perfusion fixation in brain banking: a systematic review. Acta Neuropathol. Commun. 7 (1), 146. https://doi.org/10.1186/s40478-019-0799-y.

Mercer, T.R., Qureshi, I.A., Gokhan, S., Dinger, M.E., Li, G., Mattick, J.S., Mehler, M.F., 2010. Long noncoding RNAs in neuronal-glial fate specification and oligodendrocyte lineage maturation. BMC Neurosci. 11 (1), 14. https://doi.org/10.1186/1471-2202-11-14.

Merrick, B.A., Phadke, D.P., Auerbach, S.S., Mav, D., Stiegelmeyer, S.M., Shah, R.R., Tice, R.R., Yan, W., 2013. RNA-Seq Profiling Reveals Novel Hepatic Gene Expression Pattern in Aflatoxin B1 Treated Rats. PLoS One 8 (4), e61768.

Mertelmeyer, S., Weider, M., Baroti, T., Reiprich, S., Fröb, F., Stolt, C.C., Wagner, K.-U., Wegner, M., 2020. The transcription factor Sox10 is an essential determinant of branching morphogenesis and involution in the mouse mammary gland. Sci. Rep. 10 (1), 17807. https://doi.org/10.1038/s41598-020-74664-y.

Michael Deans, P.J., Brennand, K.J., 2021. Applying stem cells and CRISPR engineering to uncover the etiology of schizophrenia. Curr. Opin. Neurobiol. 69, 193–201. https://doi.org/10.1016/j.conb.2021.04.003.

Mifsud, B., Tavares-Cadete, F., Young, A.N., Sugar, R., Schoenfelder, S., Ferreira, L., Wingett, S.W., Andrews, S., Grey, W., Ewels, P.A., Herman, B., Happe, S., Higgs, A., LeProust, E., Follows, G.A., Fraser, P., Luscombe, N.M., Osborne, C.S., 2015. Mapping long-range promoter contacts in human cells with high-resolution capture Hi-C. Nat. Genet. 47 (6), 598–606.

Mimitou, E.P., Cheng, A., Montalbano, A., Hao, S., Stoeckius, M., Legut, M., Roush, T., Herrera, A., Papalexi, E., Ouyang, Z., Satija, R., Sanjana, N.E., Koralov, S.B., Smibert, P., 2019. Multiplexed detection of proteins, transcriptomes, clonotypes and CRISPR perturbations in single cells. Nat. Methods 16 (5), 409–412.

Moghaddam, B., Javitt, D., 2012. From revolution to evolution: The glutamate hypothesis of schizophrenia and its implication for treatment. In. Neuropsychopharmacology 37 (1), 4–15.

Morris, R.G.M., Anderson, E., Lynch, G.S., Baudry, M., 1986. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 319 (6056), 774–776. https://doi.org/10.1038/319774a0.

Mu, Q., Chen, Y., Wang, J., 2019. Deciphering Brain Complexity Using Single-cell Sequencing. Genomics Proteomics Bioinformatics 17 (4), 344–366. https://doi.org/10.1016/j.gpb.2018.07.007.

Myers, S. J., Yuan, H., Kang, J. Q., Tan, F. C. K., Traynelis, S. F., & Low, C. M. (2019). Distinct roles of GRIN2A and GRIN2B variants in neurological conditions [version 1; peer review: 2 approved]. In *F1000Research* (Vol. 8). 10.12688/f1000research.18949.1.

Naghavi-Gargari, B., Zahirodin, A., Ghaderian, S.M.H., Shirvani-Farsani, Z., 2019. Significant increasing of DISC2 long non-coding RNA expression as a potential biomarker in bipolar disorder. Neurosci. Lett. 696, 206–211. https://doi.org/10.1016/j.neulet.2018.12.044.

Nestler, E.J., Hyman, S.E., 2010. Animal models of neuropsychiatric disorders. Nat. Neurosci. 13 (10), 1161–1169. https://doi.org/10.1038/nn.2647.

Ni, C., Jiang, W., Wang, Z., Wang, Z., Zhang, J., Zheng, X., Liu, Z., Ou, H., Jiang, T., Liang, W., Wu, F., Li, Q., Hou, Y., Yang, Q., Guo, B., Liu, S., Li, S., Li, S., Yang, E., Zhao, C., 2021. LncRNA-AC006129.1 reactivates a SOCS3-mediated anti-inflammatory response through DNA methylation-mediated CIC downregulation in schizophrenia. Mol. Psychiatry 26 (8), 4511–4528. https://doi.org/10.1038/s41380-020-0662-3.

Noh, H., Shao, Z., Coyle, J.T., Chung, S., 2017. Modeling schizophrenia pathogenesis using patient-derived induced pluripotent stem cells (iPSCs). Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1863 (9), 2382–2387.

Notaras, M., Lodhi, A., Fang, H., Greening, D., Colak, D., 2021. The proteomic architecture of schizophrenia iPSC-derived cerebral organoids reveals alterations in GWAS and neuronal development factors. Transl. Psych. 11 (1) https://doi.org/10.1038/s41398-021-01664-5.

O'Brien, J., Hayder, H., Zayed, Y., Peng, C., 2018. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Front. Endocrinol. 9, 402. https://doi.org/10.3389/fendo.2018.00402.

Olah, M., Menon, V., Habib, N., Taga, M.F., Ma, Y., Yung, C.J., Cimpean, M., Khairallah, A., Coronas-Samano, G., Sankowski, R., Grün, D., Kroshilina, A.A., Dionne, D., Sarkis, R.A., Cosgrove, G.R., Helgager, J., Golden, J.A., Pennell, P.B., Prinz, M., Vonsattel, J.P.G., Teich, A.F., Schneider, J.A., Bennett, D.A., Regev, A., Elyaman, W., Bradshaw, E.M., De Jager, P.L., 2020. Single cell RNA sequencing of human microglia uncovers a subset associated with Alzheimer's disease. Nat. Commun. 11 (1) https://doi.org/10.1038/s41467-020-19737-2.

Oudelaar, A.M., Higgs, D.R., 2021. The relationship between genome structure and function. Nat. Rev. Genet. 22 (3), 154–168. https://doi.org/10.1038/s41576-020-00303-x.

Panigrahi, A., O'Malley, B.W., 2021. Mechanisms of enhancer action: the known and the unknown. Genome Biol. 22 (1), 108. https://doi.org/10.1186/s13059-021-02322-1.

Pekowska, A., Benoukraf, T., Zacarias-Cabeza, J., Belhocine, M., Koch, F., Holota, H., Imbert, J., Andrau, J.C., Ferrier, P., Spicuglia, S., 2011. H3K4 tri-methylation provides an epigenetic signature of active enhancers. EMBO J. 30 (20) https://doi.org/10.1038/emboj.2011.295.

Peng, H., Xie, P., Liu, L., Kuang, X., Wang, Y., Qu, L., Gong, H., Jiang, S., Li, A., Ruan, Z., Ding, L., Yao, Z., Chen, C., Chen, M., Daigle, T.L., Dalley, R., Ding, Z., Duan, Y., Feiner, A., Zeng, H., 2021. Morphological diversity of single neurons in molecularly defined cell types. Nature 598 (7879), 174–181. https://doi.org/10.1038/s41586-021-03941-1.

Piwecka, M., Rajewsky, N., Rybak-Wolf, A., 2023. Single-cell and spatial transcriptomics: deciphering brain complexity in health and disease. Nat. Rev. Neurol. 19 (6), 346–362. https://doi.org/10.1038/s41582-023-00809-y.

Pollen, A.A., Nowakowski, T.J., Shuga, J., Wang, X., Leyrat, A.A., Lui, J.H., Li, N., Szpankowski, L., Fowler, B., Chen, P., Ramalingam, N., Sun, G., Thu, M., Norris, M., Lebofsky, R., Toppani, D., Kemp, D.W., Wong, M., Clerkson, B., Jones, B.N., Wu, S., Knutsson, L., Alvarado, B., Wang, J., Weaver, L.S., May, A.P., Jones, R.C., Unger, M. A., Kriegstein, A.R., West, J.A.A., 2014. Low-coverage single-cell mRNA sequencing reveals cellular heterogeneity and activated signaling pathways in developing cerebral cortex. Nat. Biotechnol. 32 (10), 1053–1058.

PsychENCODE Consortium, Akbarian, S., Liu, C., Knowles, J. A., Vaccarino, F. M., Farnham, P. J., Crawford, G. E., Jaffe, A. E., Pinto, D., Dracheva, S., Geschwind, D. H., Mill, J., Nairn, A. C., Abyzov, A., Pochareddy, S., Prabhakar, S., Weissman, S., Sullivan, P. F., State, M. W., … Sestan, N. (2015). The PsychENCODE project. *Nature Neuroscience*, *18*(12), 1707–1712. 10.1038/nn.4156.

Purves-Tyson, T.D., Owens, S.J., Rothmond, D.A., Halliday, G.M., Double, K.L., Stevens, J., McCrossin, T., Shannon Weickert, C., 2017. Putative presynaptic dopamine dysregulation in schizophrenia is supported by molecular evidence from post-mortem human midbrain. Transl. Psychiatry 7 (1), e1003.

Qian, X., Nguyen, H.N., Jacob, F., Song, H., Ming, G., 2017. Using brain organoids to understand Zika virus-induced microcephaly. Development 144 (6), 952–957. https://doi.org/10.1242/dev.140707.

Qian, X., Jacob, F., Song, M.M., Nguyen, H.N., Song, H., Ming, G., 2018. Generation of human brain region–specific organoids using a miniaturized spinning bioreactor. Nat. Protoc. 13 (3), 565–580. https://doi.org/10.1038/nprot.2017.152.

Ragan, C., Patel, K., Edson, J., Zhang, Z.-H., Gratten, J., Mowry, B., 2017. Small non-coding RNA expression from anterior cingulate cortex in schizophrenia shows sex specific regulation. Schizophr. Res. 183, 82–87. https://doi.org/10.1016/j.schres.2016.11.024.

Ragland, J.D., Yoon, J., Minzenberg, M.J., Carter, C.S., 2007. Neuroimaging of cognitive disability in schizophrenia: Search for a pathophysiological mechanism. In. Int. Rev. Psychiatry 19 (4), 417–427.

Raha, D., Hong, M., Snyder, M., 2010. ChIP-Seq: A Method for Global Identification of Regulatory Elements in the Genome. CP Molecular Biology 91 (1).

Reichow, S.L., Hamma, T., Ferré-D'Amaré, A.R., Varani, G., 2007. The structure and function of small nucleolar ribonucleoproteins. Nucleic Acids Res. 35 (5), 1452–1464. https://doi.org/10.1093/nar/gkl1172.

Ren, Y., Cui, Y., Li, X., Wang, B., Na, L., Shi, J., Wang, L., Qiu, L., Zhang, K., Liu, G., Xu, Y., 2015. A co-expression network analysis reveals lncRNA abnormalities in peripheral blood in early-onset schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 63, 1–5. https://doi.org/10.1016/j.pnpbp.2015.05.002.

Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J.L., Kähler, A.K., Akterin, S., Bergen, S. E., Collins, A.L., Crowley, J.J., Fromer, M., Kim, Y., Lee, S.H., Magnusson, P.K.E., Sanchez, N., Stahl, E.A., Williams, S., Wray, N.R., Xia, K., Bettella, F., Borglum, A.D., Bulik-Sullivan, B.K., Cormican, P., Craddock, N., de Leeuw, C., Durmishi, N., Gill, M., Golimbet, V., Hamshere, M.L., Holmans, P., Hougaard, D.M., Kendler, K.S., Lin, K., Morris, D.W., Mors, O., Mortensen, P.B., Neale, B.M., O'Neill, F.A., Owen, M.J., Milovancevic, M.P., Posthuma, D., Powell, J., Richards, A.L., Riley, B.P., Ruderfer, D., Rujescu, D., Sigurdsson, E., Silagadze, T., Smit, A.B., Stefansson, H., Steinberg, S., Suvisaari, J., Tosato, S., Verhage, M., Walters, J.T., Bramon, E., Corvin, A.P., O'Donovan, M.C., Stefansson, K., Scolnick, E., Purcell, S., McCarroll, S. A., Sklar, P., Hultman, C.M., Sullivan, P.F., 2013. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat. Genet. 45 (10), 1150–1159.

Roussos, P., & Haroutunian, V. (2014). Schizophrenia: Susceptibility genes and oligodendroglial and myelin related abnormalities. In *Frontiers in Cellular Neuroscience* (Vol. 8, Issue JAN). 10.3389/fncel.2014.00005.

Roussos, P., Giakoumaki, S.G., Adamaki, E., Anastasios, G., Nikos, R.K., Bitsios, P., 2011. The Association of Schizophrenia Risk D-Amino Acid Oxidase Polymorphisms With Sensorimotor Gating, Working Memory and Personality in Healthy Males. Neuropsychopharmacology 36 (8), 1677–1688. https://doi.org/10.1038/npp.2011.49.

Roussos, P., Katse, P., Davis, K.L., Bitsios, P., Giakoumaki, S.G., Jogia, J., Rozsnyai, K., Collier, D., Frangou, S., Siever, L.J., Haroutunian, V., 2012. Molecular and genetic evidence for abnormalities in the nodes of ranvier in schizophrenia. Arch. Gen. Psychiatry 69 (1). https://doi.org/10.1001/archgenpsychiatry.2011.110.

Roussos, P., Mitchell, A., Voloudakis, G., Fullard, J., Pothula, V., Tsang, J., Stahl, E., Georgakopoulos, A., Ruderfer, D., Charney, A., Okada, Y., Siminovitch, K., Worthington, J., Padyukov, L., Klareskog, L., Gregersen, P., Plenge, R., Raychaudhuri, S., Fromer, M., Purcell, S., Brennand, K.J., Robakis, N., Schadt, E., Akbarian, S., Sklar, P., 2014. A role for noncoding variation in schizophrenia. Cell Rep. 9 (4), 1417–1429.

Ruzicka, W. B., Mohammadi, S., Fullard, J. F., Davila-Velderrain, J., Subburaju, S., Tso, D. R., Hourihan, M., Jiang, S., Lee, H.-C., Bendl, J., Consortium, P., Voloudakis, G., Haroutunian, V., Hoffman, G. E., Roussos, P., & Kellis, M. (2022). Single-cell multi-cohort dissection of the schizophrenia transcriptome. *MedRxiv*, 2022.08.31.22279406. 10.1101/2022.08.31.22279406.

Salles, A., Bjaalie, J.G., Evers, K., Farisco, M., Fothergill, B.T., Guerrero, M., Maslen, H., Muller, J., Prescott, T., Stahl, B.C., Walter, H., Zilles, K., Amunts, K., 2019. The Human Brain Project: Responsible Brain Research for the Benefit of Society. Neuron 101 (3), 380–384. https://doi.org/10.1016/j.neuron.2019.01.005.

Samantara, K., Shiv, A., de Sousa, L.L., Sandhu, K.S., Priyadarshini, P., Mohapatra, S.R., 2021. A comprehensive review on epigenetic mechanisms and application of epigenetic modifications for crop improvement. Environ. Exp. Bot. 188, 104479.

Sano, H., Chiken, S., Hikida, T., Kobayashi, K., Nambu, A., 2013. Signals through the Striatopallidal Pathway Stop Movements by Phasic Excitation in the Substantia Nigra. J. Neurosci. 33 (17), 7583–7594. https://doi.org/10.1523/JNEUROSCI.4932-12.2013.

Sarkar, A., Stephens, M., 2021. Separating measurement and expression models clarifies confusion in single-cell RNA sequencing analysis. Nat. Genet. 53 (6), 770–777. https://doi.org/10.1038/s41588-021-00873-4.

Sato, S., Arimura, Y., Kujirai, T., Harada, A., Maehara, K., Nogami, J., Ohkawa, Y., Kurumizaka, H., 2019. Biochemical analysis of nucleosome targeting by Tn5 transposase. Open Biol. 9 (8) https://doi.org/10.1098/rsob.190116.

Schoenfelder, S., Furlan-Magaril, M., Mifsud, B., Tavares-Cadete, F., Sugar, R., Javierre, B.-M., Nagano, T., Katsman, Y., Sakthidevi, M., Wingett, S.W., Dimitrova, E., Dimond, A., Edelman, L.B., Elderkin, S., Tabbada, K., Darbo, E., Andrews, S., Herman, B., Higgs, A., LeProust, E., Osborne, C.S., Mitchell, J.A., Luscombe, N.M., Fraser, P., 2015. The pluripotent regulatory circuitry connecting promoters to their long-range interacting elements. Genome Res. 25 (4), 582–597.

Sekar, A., Bialas, A.R., de Rivera, H., Davis, A., Hammond, T.R., Kamitaki, N., Tooley, K., Presumey, J., Baum, M., Van Doren, V., Genovese, G., Rose, S.A., Handsaker, R.E., Daly, M.J., Carroll, M.C., Stevens, B., McCarroll, S.A., 2016. Schizophrenia risk from complex variation of complement component 4. Nature 530 (7589), 177–183.

Shukla, S., Kavak, E., Gregory, M., Imashimizu, M., Shutinoski, B., Kashlev, M., Oberdoerffer, P., Sandberg, R., Oberdoerffer, S., 2011. CTCF-promoted RNA polymerase II pausing links DNA methylation to splicing. Nature 479 (7371), 74–79. https://doi.org/10.1038/nature10442.

Shulha, H.P., Cheung, I., Guo, Y., Akbarian, S., Weng, Z., Ren, B., 2013. Coordinated Cell Type-Specific Epigenetic Remodeling in Prefrontal Cortex Begins before Birth and Continues into Early Adulthood. PLoS Genet. 9 (4), e1003433.

Singh, T., Neale, B.M., Daly, M.J., 2020. Exome sequencing identifies rare coding variants in 10 genes which confer substantial risk for schizophrenia on behalf of the Schizophrenia Exome Meta-Analysis (SCHEMA). Consortium*. *Medrxiv*.

Singh, T., Poterba, T., Curtis, D., Akil, H., Al Eissa, M., Barchas, J.D., Bass, N., Bigdeli, T. B., Breen, G., Bromet, E.J., Buckley, P.F., Bunney, W.E., Bybjerg-Grauholm, J., Byerley, W.F., Chapman, S.B., Chen, W.J., Churchhouse, C., Craddock, N., Cusick, C. M., Daly, M.J., 2022. Rare coding variants in ten genes confer substantial risk for schizophrenia. Nature 604 (7906), 509–516. https://doi.org/10.1038/s41586-022-04556-w.

Skene, N.G., Bryois, J., Bakken, T.E., Breen, G., Crowley, J.J., Gaspar, H.A., Giusti-Rodriguez, P., Hodge, R.D., Miller, J.A., Muñoz-Manchado, A.B., O'Donovan, M.C., Owen, M.J., Pardiñas, A.F., Ryge, J., Walters, J.T.R., Linnarsson, S., Lein, E.S., Sullivan, P.F., Hjerling-Leffler, J., 2018. Genetic identification of brain cell types underlying schizophrenia. Nat. Genet. 50 (6), 825–833.

Smalheiser, N.R., Lugli, G., Zhang, H., Rizavi, H., Cook, E.H., Dwivedi, Y., Mukhopadhyay, P., 2014. Expression of microRNAs and Other Small RNAs in Prefrontal Cortex in Schizophrenia, Bipolar Disorder and Depressed Subjects. PLoS One 9 (1), e86469.

Smith, C., Bolton, A., Nguyen, G., 2010. Genomic and Epigenomic Instability, Fragile Sites, Schizophrenia and Autism. Curr. Genomics 11 (6). https://doi.org/10.2174/138920210793176001.

Song, L., & Crawford, G. E. (2010). DNase-seq: A high-resolution technique for mapping active gene regulatory elements across the genome from mammalian cells. *Cold Spring Harbor Protocols*, *5*(2). 10.1101/pdb.prot5384.

Song, L., Pan, S., Zhang, Z., Jia, L., Chen, W.-H., Zhao, X.-M., 2021. STAB: a spatio-temporal cell atlas of the human brain. Nucleic Acids Res. 49 (D1), D1029–D1037. https://doi.org/10.1093/nar/gkaa762.

Stilo, S.A., Murray, R.M., 2019. Non-Genetic Factors in Schizophrenia. Curr. Psychiatry Rep. 21 (10), 100. https://doi.org/10.1007/s11920-019-1091-3.

Sullivan, P.F., Agrawal, A., Bulik, C.M., Andreassen, O.A., Børglum, A.D., Breen, G., Cichon, S., Edenberg, H.J., Faraone, S.V., Gelernter, J., Mathews, C.A., Nievergelt, C. M., Smoller, J.W., O'Donovan, M.C., 2018. Psychiatric Genomics: An Update and an Agenda. Am. J. Psychiatry 175 (1), 15–27.

Takahashi, N., Sakurai, T., Davis, K.L., Buxbaum, J.D., 2011. Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia. Prog. Neurobiol. 93 (1), 13–24. https://doi.org/10.1016/j.pneurobio.2010.09.004.

The ENCODE Project Consortium, 2012. An integrated encyclopedia of DNA elements in the human genome. Nature 489 (7414), 57–74. https://doi.org/10.1038/nature11247.

Tian, R., Gachechiladze, M.A., Ludwig, C.H., Laurie, M.T., Hong, J.Y., Nathaniel, D., Prabhu, A.V., Fernandopulle, M.S., Patel, R., Abshari, M., Ward, M.E., Kampmann, M., 2019. CRISPR Interference-Based Platform for Multimodal Genetic Screens in Human iPSC-Derived Neurons. Neuron 104 (2), 239–255.e12. https://doi.org/10.1016/j.neuron.2019.07.014.

Tian, T., Wei, Z., Chang, X., Liu, Y., Gur, R.E., Sleiman, P.M.A., Hakonarson, H., 2018. The Long Noncoding RNA Landscape in Amygdala Tissues from Schizophrenia Patients. EBioMedicine 34, 171–181. https://doi.org/10.1016/j.ebiom.2018.07.022.

Townsley, K.G., Li, A., Michael Deans, P., Fullard, J.F., Yu, A., Cartwright, S., Zhang, W., Wang, M., Voloudakis, G., Girdhar, K., Stahl, E., Akbarian, S., Zhang, B., Roussos, P., Huckins, L.M., Brennand, K.J., 2022. Convergent Impact of Schizophrenia Risk Genes. https://doi.org/10.1101/2022.03.29.486286.

Trindade, P., Nascimento, J.M., Casas, B.S., Monteverde, T., Gasparotto, J., Ribeiro, C.T., Devalle, S., Sauma, D., Moreira, J.C.F., Gelain, D.P., Porciuncula, L.O., Palma, V., Martins-de-Souza, D., Rehen, S.K., 2023. Induced pluripotent stem cell-derived astrocytes from patients with schizophrenia exhibit an inflammatory phenotype that affects vascularization. Mol. Psychiatry 28 (2), 871–882. https://doi.org/10.1038/s41380-022-01830-1.

Tripathi, A., Kar, S.K., Shukla, R., 2018. Cognitive deficits in schizophrenia: Understanding the biological correlates and remediation strategies. In. Clin. Psychopharmacol. Neurosci. 16 (1), 7–17.

Trubetskoy, V., Pardiñas, A.F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T.B., Bryois, J., Chen, C.-Y., Dennison, C.A., Hall, L.S., Lam, M., Watanabe, K., Frei, O., Ge, T., Harwood, J.C., Koopmans, F., Magnusson, S., Richards, A.L., Sidorenko, J., van Os, J., 2022. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 604 (7906), 502–508. https://doi.org/10.1038/s41586-022-04434-5.

Vesterinen, H.M., Sena, E.S., ffrench-Constant, C., Williams, A., Chandran, S., Macleod, M.R., 2010. Improving the translational hit of experimental treatments in multiple sclerosis. Mult. Scler. J. 16 (9), 1044–1055.

Wang, C., Sun, D., Huang, X., Wan, C., Li, Z., Han, Y., Qin, Q., Fan, J., Qiu, X., Xie, Y., Meyer, C.A., Brown, M., Tang, M., Long, H., Liu, T., Liu, X.S., 2020a. Integrative analyses of single-cell transcriptome and regulome using MAESTRO. Genome Biol. 21 (1) https://doi.org/10.1186/s13059-020-02116-x.

Wang, J., Wang, F., Mai, D., Qu, S., 2020b. Molecular Mechanisms of Glutamate Toxicity in Parkinson's Disease. Front. Neurosci. 14 https://doi.org/10.3389/fnins.2020.585584.

White, R.S., Siegel, S.J., 2016. Cellular and circuit models of increased resting-state network gamma activity in schizophrenia. Neuroscience 321, 66–76. https://doi.org/10.1016/j.neuroscience.2015.11.011.

Willard, S.S., Koochekpour, S., 2013. Glutamate, glutamate receptors, and downstream signaling pathways. *Int. J. Biol. Sci.* 9 (9), 948–959.

Wilusz, J.E., Freier, S.M., Spector, D.L., 2008. 3' end processing of a long nuclear-retained noncoding RNA yields a tRNA-like cytoplasmic RNA. Cell 135 (5), 919–932. https://doi.org/10.1016/j.cell.2008.10.012.

Won, H., de la Torre-Ubieta, L., Stein, J.L., Parikshak, N.N., Huang, J., Opland, C.K., Gandal, M.J., Sutton, G.J., Hormozdiari, F., Lu, D., Lee, C., Eskin, E., Voineagu, I., Ernst, J., Geschwind, D.H., 2016. Chromosome conformation elucidates regulatory relationships in developing human brain. Nature 538 (7626), 523–527.

Worsley-Hunt, R., Bernard, V., Wasserman, W.W., 2011. Identification of cis-regulatory sequence variations in individual genome sequences. Genome Med. 3 (10), 65. https://doi.org/10.1186/gm281.

Wright, I.C., Rabe-Hesketh, S., Woodruff, P.W.R., David, A.S., Murray, R.M., Bullmore, E. T., 2000. Meta-analysis of regional brain volumes in schizophrenia. Am. J. Psychiatry 157 (1), 16–25.

Wu, H., Yin, Q.-F., Luo, Z., Yao, R.-W., Zheng, C.-C., Zhang, J., Xiang, J.-F., Yang, L., Chen, L.-L., 2016. Unusual Processing Generates SPA LncRNAs that Sequester Multiple RNA Binding Proteins. Mol. Cell 64 (3), 534–548. https://doi.org/10.1016/j.molcel.2016.10.007.

Yin, J., Lu, Y., Yu, S., Dai, Z., Zhang, F., Yuan, J., 2020. Exploring the mRNA expression level of RELN in peripheral blood of schizophrenia patients before and after antipsychotic treatment. Hereditas 157 (1), 43. https://doi.org/10.1186/s41065-020-00158-6.

Zhang, Y., Barres, B.A., 2010. Astrocyte heterogeneity: an underappreciated topic in neurobiology. Curr. Opin. Neurobiol. 20 (5), 588–594. https://doi.org/10.1016/j.conb.2010.06.005.

Zhang, Y., Chen, K., Sloan, S.A., Bennett, M.L., Scholze, A.R., O'Keeffe, S., Phatnani, H.P., Guarnieri, P., Caneda, C., Ruderisch, N., Deng, S., Liddelow, S.A., Zhang, C., Daneman, R., Maniatis, T., Barres, B.A., Wu, J.Q., 2014. An RNA-Sequencing Transcriptome and Splicing Database of Glia, Neurons, and Vascular Cells of the Cerebral Cortex. J. Neurosci. 34 (36), 11929–11947. https://doi.org/10.1523/JNEUROSCI.1860-14.2014.

Zhang, Z., Yang, C., Zhang, X., 2022. scDART: integrating unmatched scRNA-seq and scATAC-seq data and learning cross-modality relationship simultaneously. Genome Biol. 23 (1) https://doi.org/10.1186/s13059-022-02706-x.

Zhong, W.X., Dong, Z.F., Tian, M., Cao, J., Xu, L., Luo, J.H., 2006. N-methyl-D-aspartate receptor-dependent long-term potentiation in CA1 region affects synaptic expression of glutamate receptor subunits and associated proteins in the whole hippocampus. Neuroscience 141 (3), 1399–1413. https://doi.org/10.1016/j.neuroscience.2006.04.070.

Zhu, K., Bendl, J., Rahman, S., Vicari, J., Coleman, C., Clarence, T., Latouche, O., Tsankova, N. M., Li, A., Brennand, K., Lee, D., Yuan, G.-C., Fullard, J. F., & Roussos, P. (2022). *Multi-omic profiling of the developing human cerebral cortex at the single cell level*.

Zhu, K., Bendl, J., Rahman, S., Vicari, J. M., Coleman, C., Clarence, T., Latouche, O., Tsankova, N. M., Li, A., Brennad, K. J., Lee, D., Yuan, G.-C., Fullard, J. F., & Roussos, P. (2022). *Multi-omic profiling of the developing human cerebral cortex at the single cell level*.

Ziffra, R.S., Kim, C.N., Ross, J.M., Wilfert, A., Turner, T.N., Haeussler, M., Casella, A.M., Przytycki, P.F., Keough, K.C., Shin, D., Bogdanoff, D., Kreimer, A., Pollard, K.S., Ament, S.A., Eichler, E.E., Ahituv, N., Nowakowski, T.J., 2021. Single-cell epigenomics reveals mechanisms of human cortical development. Nature 598 (7879), 205–213.