The Role of Genetic Mutation on Schizophrenia: A Basic Review Prior to Pharmacogenomics

Dhea Nur Hikmah, Alfian Syarifuddin, Setiyo Budi Santoso, Ratna Wijayatri, and Imron Wahyu Hidayat (✉)

Universitas Muhammadiyah Magelang, Magelang, Indonesia
imronwh@unimma.ac.id

Abstract. A bioinformatic approach is used to identify indications of reposition drug. It drives newer methods to treating schizophrenia by comparing the binding profiles of currently available clinical compounds to targets or groups of targets derived based on genome-wide association studies (GWAS). Here in, we present the molecular expression of schizophrenia due to polymorphism. The study involves papers indexed by Scopus, and the search uses a combination of the following keyword variants; "GWAS" AND "genom" AND schizophrenia, "GWAS" AND "repurposing drug" AND "schizophrenia". This study only used original articles in English peer-reviewed journals published during 2022. Thus, the screening results of sources were narrowed to 5 original articles that met the inclusion criteria. We identified 9 genes involved in pathophysiology of schizophrenia. Interestingly, a number of genes have been discovered as being the druggable target. Publications on drug repurposing for schizophrenia treatment suggest possible medication candidates such as verapamil, cinnarizine, nicotine, varenicline, galantamine, and DPP4 inhibitors metoclopramide, trifluoperazine, and neratinib.

Keywords: Bioinformatical, GWAS, Genome.

1 Introduction

Schizophrenia (SCZ) has been described as a disorder of abnormal cortical-subcortical connection and defective synaptic plasticity, has a complex biological architecture and a multigenic etiopathogenesis that likely involves multiple biological pathways [1]. According to the functional disconnectivity theory, a lack of connection between scattered brain regions could be the cause of schizophrenia symptoms [2]. Although environmental and genetic variables could contribute to the creation of SCZ, genetic factors appear to have a considerable impact. With an estimated heritability of up to 70%, data from twin, family, and adoption studies in particular suggests to a significant genetic component. The "glutamatergic dysfunction hypothesis of SCZ" was developed in recent years as a result of various in vivo and post-mortem receptor investigations that showed a severe disruption of the glutamatergic system in people with SCZ. A growing body of empirical research supports this hypothesis, which focuses on abnormalities in the genes involved in the glutamatergic system, including those coding

Z. B. Pambuko et al. (eds.), *Proceedings of the 4th Borobudur International Symposium on Humanities and Social Science 2022 (BIS-HSS 2022)*, Advances in Social Science, Education and Humanities Research 778,
https://doi.org/10.2991/978-2-38476-118-0_96

for glutamate receptors (AMPA, NMDA, kainite, and metabotropic receptors). It also suggests a connection between this neurotransmitter and SCZ [3].

Data demonstrating the chance of less than 1% of people in the general population have schizophrenia and grow progressively if just one (7%) or both parents (27.3%) are condition further illustrate the genetic liability. The interaction of several genes that primarily affect two distinct processes results in a genetic risk for schizophrenia. [4]. However, it's crucial to keep in mind that just 3.8% of family groupings afflicted more than one family member is impacted by schizophrenia, and that 90% of adults with the disorder do not have a parent who also has the condition. According to this data, the idea maybe there are additional factors than genetic risk determining whether a person develops schizophrenia and that the illness only manifests in people who have a genetic propensity for the illness and has been exposed to the environment triggers is strongly supported [5].

Determining the genes that support the hereditary vulnerability due to the syndrome has thus received a lot of attention in an attempt to comprehend the epidemiology of the condition. A complicated clinical profile that encompasses cognitive impairment, negative symptoms like anhedonia, social disengagement, and apathy, as well as positive symptoms like delusions and hallucinations [6]. Many common, small-effect variants as well as uncommon, moderate-risk variants contribute to the complex genetic disorder known as schizophrenia, which has a strong polygenic component. Psychiatric Genomics Consortium (PGC) the schizophrenia group's GWAS meta-analysis in schizophrenia has specifically found 128 independent associations the dopamine D2 receptor locus and numerous additional neurotransmitter genes are located in 108 genomic regions, particularly calcium and glutamate are those engaged in the central nervous system (CNS) signaling, that meet genome-wide significance. By comparing the binding profiles of currently available clinical compounds to targets or groups of targets derived this strategy could be applied to identify potential drug reposition signals from genome-wide association studies (GWAS) or other genetic research to develop novel treatment paradigms for schizophrenia [7]. Finding possible targets for medicinal therapies is one of GWAS's main goals. [8].

Psychiatric Genomics Consortium (PGC) Schizophrenia Working Group have discovered several substantial genome-wide association around schizophrenia and genes related to glutamatergic neurotransmission [9]. Given many of these challenges, there has been a resurgence of interest in repurposing drug, or the discovery of new therapeutic applications for medications with regulatory approval, in schizophrenia in recent years. The benefit of this approach is that the drug candidate already-present dosing, pharmacokinetic, toxicology, and medicinal chemistry profiles help to speed upclinical studies for the new indication are needed to reduce the high attrition rate (90%) that most novel drug entities have, especially those with neuropsychiatric indications. This is reminiscent of the 1950s in many ways, when the molecular basis for the majority of modern treatments for schizophrenia was discovered through chance clinical evaluation of the antipsychotic effects of prescribed medications for other purposes, such as the pre-anesthetic chlorpromazine [10].

In this study, GWAS is used to identify indications for repositioning novel drugs to be used for treating schizophrenia by dressing the binding profile of clinical compounds.

2 Method

The study involves literature indexed by the databases Scopus and Pubmed, and the search uses a combination the following keyword variant; “GWAS” AND “genom” AND “Schizophrenia” and “GWAS” AND “repurposing drug” AND “Schizophrenia”. This study only used original articles in English language, which were from peer-reviewed journals published in 2022 (**Error! Reference source not found.**).

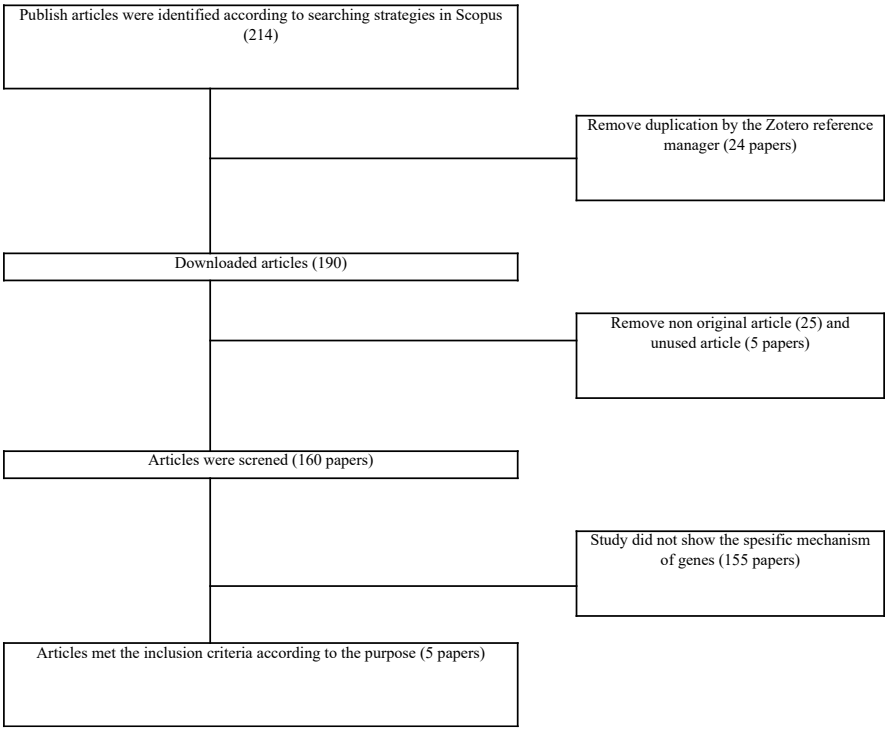

Fig. 1. Literatures study of workflow

3 Result and Discussion

3.1 Main Result

We identified 9 genes involved in the pathophysiology of schizophrenia, three of which are pathways, including Ras GRP1-ERK-MTOR Pathway, and six additional genes, which include HTR3A, HTR3B, SCN2B, KCNAB2, CAMKA2A, and CAMKA1G [4],

[6], [11]. Interestingly, a number of genes, including CACNA1C, CACNB2, CACNA1I, CHRM4 CHRNA3/CHRNB4, GRIA1, GRIN2A, and GRM3, have been discovered as being the druggable target [12]. Publications on drug repurposing for schizophrenia treatment suggest possible medication candidates such as verapamil, cinnarizine, nicotine, varenicline, galantamine, and DPP4 inhibitors metoclopramide, trifluoperazine, and neratinib [4], [11] (**Error! Reference source not found.**).

Table 1. The review of literature's primary findings

No	Topic	Original Indication	References
1.	Genes expression in schizophrenia pathology	Ras GRP1-ERK-MTOR Pathway	[6]
2.	Genes expression in schizophrenia pathology	HTR3A, HTR3B,	[11]
3.	Genes expression in schizophrenia pathology	SCN2B, KCNAB2, CAMKA2A, CAMKA1G,	[4]
4.	The druggable Target Genes	CACNA1C, CACNB2, CACNA1I, CHRM4 CHRNA3/CHRNB4, GRIA1, GRIN2A, GRM3	[12]
5.	Drug repurposing for schizophrenia	verapamil, cinnarizine, nikotin, varenicline, galantamine, and DPP4 inhibitor	[13]
6.	Drug repurposing for schizophrenia	Dopamin antagonis reseptor (metoclopramide and trifluoperazine), D2 agonis (Trifluoperazine), Tyrosine-kinase inhibitor (neratinib)	[11]

Abbreviations: calcium voltage-gated channel auxiliary CACNA1C (subunit alpha 1C), calcium voltage-gated channel auxiliary subunit beta 2 (CACNB2), calcium voltage-gated channel auxiliary subunit alpha 1I (CACNA1I), calcium/calmodulin dependent protein kinase 2 alpha (CAMKA2A), calcium/calmodulin dependent protein kinase1G (CAMKA1G), cholinergic receptor muscarinic 4 (CHRM4), CHRNA3 (cholinergic receptor nicotinic alpha 3 subunit), CHRNB4 (cholinergic receptor nicotinic beta 4 subunit), Dipeptidyl Peptidase 4 (DPP4), glutamate ionotropic receptor AMPA type subunit 1 (GRIA1), glutamate ionotropic receptor NMDA type subunit 2A (GRIN2A), glutamate metabotropic receptor 3 (GRM3), 5-hydroxytryptamie receptor 3A (HTR3A), KCNAB2 (potassium voltage-gated channel subfamily a regulatory beta subunit 2), (SCN2B) sodium voltage-gated channel beta subunit 2.

3.2 The pathophysiology of schizophrenia due to gene expression

Serotonergic (serotonin, 5-hydroxytryptamine, 5-HT) it appears that neurotransmission is implicated pathophysiology of schizophrenia [14]. The brain's serotonin system plays an important part in the emergence of psychiatric symptoms. Two subunits (HTR3A and HTR3B) of the serotonin ion-gated channel HTR3 are responsible for excitatory fast depolarization events. HTR3A is found in the limbic area, which includes the hippocampus and amygdala, and has been linked the functions of the HPA (hypothalamic-pituitary-adrenal) axis, anxiety, and cognition [15]. Serotonin receptors 3A and 3B a connection between schizophrenia and recent genetic association studies [16]. HTR3A in schizophrenia patients had a gene that codes for the serotonin transporter SLC6A4 with MetS.[14]. HTR3B genetic polymorphisms may have an impact on serotonin signalling, HTR3 complex expression or function [17]. A prior study on HTR3B found that the C allele of rs10789970 was linked to inadequate focus and attention people with schizophrenia [18].

CAMKIG promoting dendritic outgrowths in cortical neurons [19] and decreasing activity of parvalbumin neurons in schizophrenia, while the most severely impacted neurons in schizophrenia are those that express the Ca2+-binding protein parvalbumin [20]. Stress regulates CAMK1G expression, which is reliant on glucocorticoid receptor activation. We presumed that CAMK1G might be involved in signalling processes that support either adaptive or maladaptive responses to stress as it is widely expressed in limbic system neuronal cells [21]. Indicating that CAM kinase cascade could be crucial in the sensitivity to schizophrenia, CAMK2A, a member of the CAM-dependent protein kinases subfamily, was found to be one of the top candidate genes for schizophrenia [22]. The brain's "dopamine-mediated NMDA receptor trafficking" mechanisms are activated by an increase in the extracellular concentration of dopamine, which is mediated by CAMK2A. NMDA receptors are glutamate-gated cation channels involved in synaptic response regulation [23]. When NMDA receptors are activated, calcium (Ca2 +) enters the postsynaptic area, activating various signalling cascades [24].

The KCNAB2 gene encodes a voltage-gated potassium channel that modulates neurotransmitter release and neuronal excitability.. The protein is highly expressed in the hippocampus, in mice, the outcome of the gene's deletion in abnormal amygdala neuron excitability as well as deficiencies in associative fear conditioning, which is also present in depressive patients and is thought to predict later aggressive behaviour in young children [25]. KCNA2, a key potassium channel subunit who expression is controll in reaction to neuropathic pain and peripheral nerve damage by the overlapping antisense RNA KCNA2-AS [26]. NEAT1 binds ion channel modulators like KCNAB2, a protein that interacts with potassium channels and is associated with neuronal excitability, and its expression is decreased in response to acute neuronal activity [27].

SCN2B, a gene key in the maintenance of standard physiological processes hippocampus and prefrontal cortex, may be linked to prefrontal cortex ageing the memories impairment [28], while not part of the major network, it was upregulated on the schizophrenia [29]. The sodium-potassium pump set consists of 14 genes, ten of which encode alpha subunits responsible for the formation of action potentials, and four of which together with subunits alpha affect cellular and gating excitability. There are

lesser beta subunits, and only SCN2B and SCN4B's paralog conservation scores are known all ten alpha subunits have paralog conservation ratings [30].

3.3 The druggable target genes

RasGRP1, a member of a class nucleotide exchange factors (GEFs), which are widely expressed in hematopoietic cells, are a class of proteins called guanine, has been linked to leukemia and lupus erythematosus. It is also recognized to contribute to the growth of T and B cells. People with schizophrenia have higher levels of RasGRP1, which is found in the DLPFC (dorsolateral prefrontal cortex) and blood vessels. RasGRP1 acts similarly to Dopamine in causing schizophrenia by regulating ERK (extracellular signal-regulated kinases) and mammalian target of rapamycin kinase (mTOR) [6]. The major role of ERK (extracellular signal-regulated kinases) is to increase the long-term flexibility of neurons, but in persons with schizophrenia, the quantity of ERK might increase more than in normal people, interfering with good cognitive function of the brain [31], [32]. Meanwhile, mTOR aids neurons in the process of autophagy when nutrients are scarce. When RasGRP1 levels rise, mTOR levels rise as well, interfering with the autophagy mechanism in which neurons increase autophagy activity, which can enhance nutrition, causing toxicity and nerve damage [33], [34].

CACNA1C is a gene that causes neurodevelopmental or neurodevelopmental abnormalities that lead to schizophrenia [35]–[37]. CACNA1C is translate by EZH2 [35]. In connection to the occurrence of schizophrenia, CACNA1C is a gene that encodes an alpha subunit, which leads in increased channel permeability, allowing extra neurotransmitters to be released [36], [37]. The CACNA1C gene is commonly found in SNPs rs 1006737 (1,2,3), rs 2007044 and rs 4765913 [37] CACNA1I is a gene that promotes the opening of Cav 3.3 (Calcium Channel) [38] which is a neuronal voltage-gated calcium channel that underpins a subtype of T-type current critical for neuronal excitability in the thalamic reticular nucleus and other brain regions [38]. This, in turn, causes the release of GABAergic neurons in the thalamus reticular nucleus (TRN), which disrupts sleep spadle formation and leads to thalamocortical network dysfunction [39]. This gene's distribution is most frequent in the brain, and the Chinese population is one of the most vulnerable communities to it [40]. CACNB2 enhances the opening of the B2 subunit vgcc (Voltage-gated calcium channel) [41], whereas a trans-Golgi network is encoded by ARL5B localised a little G protein that has been called a crucial retrograde membrane transport regulator [42], which in turn triggers retrograde membrane transport. Axonal transport deficiency is also associated with ARL5B [42]. Thus, calcium channel blockers can inhibit the CACNB2 gene [43].

CHRM4 plays a significant function in the cholinergic regulation of dopamine release. As a result, the control of CHRM4 signalling may have also contributed to the psychotic schizophrenia-related symptoms [44]. Notably, novel medicines that directly activate CHRM1 and CHRM4 are being developed, and are being considered as potential therapies for schizophrenia [45]. Previous studies have linked schizophrenia to muscarinic M4 receptors (CHRM4). This disease was discovered to be significantly connected to the rs2067482 polymorphism in particular. Delusions in schizophrenia, according to popular belief, are caused by aberrant salience (amygdala function) driven

by dopaminergic hyperactivity (function of the midbrain). We hypothesised that the fundamental mechanism could be the opposite way around, with amygdala and hippocampus dysfunction activating midbrain monoaminergic areas, which activate pleasure and happiness circuits. The role of CHRM4 in the activity of fibres originating in the amygdala and hippocampus and projecting to the ventral striatum and/or to monoaminergic midbrain locations via the habenula may be important in explaining schizophrenia delusions [46].

The components of the CHRNA5-CHRNA3-CHRB4 gene cluster, which codes for the nicotinic acetylcholine receptor (nAChR). [47]. Acetylcholine (ACh) release is important for cognitive functioning in the PFC. The 5 nAChR subunit is encoded by the CHRNA5 gene. The PFC has the 5 nAChR subunit. The failure of ACh signalling nAChRs in the PFC that contain the 5 subunit may help the reduced intellectual skills seen in schizophrenia (SCZ) [48]. More research is needed to understand the actual implications of cis-acting mutations at the CHRNA5/A3/B4 locus on TCF4 and other transcriptional factors in schizophrenia (SCZ) [49].

GRIA1 is mainly found in the hippocampus and frontal cortex, two regions of brain that are crucial for the formation and maintenance of spatial memory [50]. Schizophrenia is significantly connected to decreased synaptic plasticity and glutamatergic transmission in the hippocampus. Recent GWAS have identified GRIA1, the gene encoding amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GLUA1, as a possible schizophrenia risk gene. GRIA1 mRNA and protein levels were similarly found to be lower in post-mortem hippocampus tissue from schizophrenia patients [51]. The glutamate receptor's AMPA subtype's GluA1 component is encoded by the gene GRIA1. This discovery strengthens the body of research suggesting that AMPARs and NMDARs play a role in the disease. Particularly pertinent in this context is the evidence that GluA1 mRNA and GluA1 changes, as well as AMPAR binding sites, occur in the hippocampus of schizophrenia patients that do not appear to be connected to antipsychotic medication [52].

One hypothesis for the pathophysiology of schizophrenia N-methyl-D-aspartic acid receptors (NMDArs) and its endogenous co-agonist D-serine (D-Ser) are a possible mediator of aberrant glutamate neurotransmission. D-Ser, an endogenous co-agonist of NMDA, is located in the mammalian brain and has been utilized to treat schizophrenia due to alterations in control of the expression of NMDAr subunit genes caused by GRIN2A gene promoter polymorphism [53]. The failure of the glutamate receptor N-methyl-D-aspartate is also being investigated in relation to the specifics of the course of schizophrenia. Thus, earlier research has found a link between the severity of schizophrenia's chronic outcome and the length of the GRIN2A variable polymorphism (GT)n repeated. This could imply that NMDA receptor subunit malfunction can be a schizophrenia's developmental stimulant , and that major mutations in the GRIN2B and GRIN2A genes can modify early or late onset [54]. Grin2a deficiency alters convergent neuronal networks, probably involving gamma oscillatory cell types, PV+ interneurons and excitation neurons, in circuits. [55].

GRM3 expression in astrocytic cells is required to protect neurons against NMDA-induced neurotoxicity. This means that diminished GRM3 functionality, which may produce hyper glutamatergic signaling, may also result in greater damage to the neurons

as a result of the abnormal signalling exhibited in schizophrenia [56]. In a recently revealed genome-wide association analysis of schizophrenia, rs12704290, a polymorphism in A marker near GRM3, was one of the top hits and gained genome-wide significance (SZ) [57]. GRM3 gene polymorphisms and the risk of schizophrenia, as well as evidence that alleles giving this risk may be community specific. These findings support additional research into the understanding the mechanisms) by which GRM3 genetic polymorphism contributes to the schizophrenia risk [58].

3.4 Drug repurposing for schizophrenia

Skizofrenia treatment that uses selective calcium channel blockers (SCCB) in the form of the drug verapamil, which works through a lithium-based mechanism. Erapamil is a hypertension treatment that uses the same mechanism as selective calcium channel blockers (SCCB). Skizofrenia is also treated with the antiepilepsy medication cinnarizine. Skizofrenia can be treated by activating the nicotinic acethylcolin receptor, and the medications used are nicotin, varenicline, and galantamine, which are linked to the GABBR2, NOS1, and OPRD1 genes [13].

Skizofrenia treatment with dopamin-antagonizing reseptor antagonists such as metoclopramide and trifluoperazine. Including tyrosine kinase inhibitors such as neratinib. GWAS identified a gene associated with schizophrenia, DRD2, as well as a gene associated with SNP (single nucleotide polymorphism) involving HTR3A and HTR3B, which can be treated with metoclopramid. The next treatment is trifluoperazine, a D2 agonis that works by blocking P-gp (P-glycoprotein) activity in order to prevent schizophrenia, where ABCB1 is a gene that can activate P-gp in order to prevent schizophrenia. TKI (tyrosine-kinase inhibitor) with the example of neratinib, which has the ability to inhibit kinase with the help of GWAS and schizophrenia (FES, PRKD1, PAK6, PTK2B,TIE1) [7].

There are some diabetic medications that are safe for use with schizophrenia, such as DPP4 inhibitors like dutogliptin and aligliptin. Melanin-concentrating hormone receptor 1 (MCHR1), where antagonistic drugs are available that compete with one another to bind to the receptor, preventing MCHR1 from interacting with ATC0175 and ATC0065. Drugs that do not have these side effects or that would be able to reverse them would be a welcome addition to the pharmacopeia because current antipsychotics can cause insulin resistance [7].

4 Conclusion

We identified 9 genes involved in the pathophysiology of schizophrenia, three of which are pathways and six additional genes. Interestingly, a number of genes, including CACNA1C, CACNB2, CACNA1I, CHRM4 CHRNA3/CHRNB4, GRIA1, GRIN2A, and GRM3, have been discovered as being the druggable target. Publications on drug repurposing for schizophrenia treatment suggest possible medication candidates such as verapamil, cinnarizine, nicotine, varenicline, galantamine, and DPP4 inhibitors metoclopramide, trifluoperazine, and neratinib

References

1. A. De Rosa *dkk.*, "Machine Learning algorithm unveils glutamatergic alterations in the post-mortem schizophrenia brain," *Schizophr*, vol. 8, no. 1, hlm. 8, Feb 2022, doi: 10.1038/s41537-022-00231-1.
2. J. Mounce, L. Luo, A. Caprihan, J. Liu, N. I. Perrone-Bizzozero, dan V. D. Calhoun, "Association of GRM3 polymorphism with white matter integrity in schizophrenia," *Schizophrenia Research*, vol. 155, no. 1–3, hlm. 8–14, Mei 2014, doi: 10.1016/j.schres.2014.03.003.
3. C. Crisafulli *dkk.*, "Influence of GRIA1, GRIA2 and GRIA4 polymorphisms on diagnosis and response to antipsychotic treatment in patients with schizophrenia," *Neuroscience Letters*, vol. 506, no. 1, hlm. 170–174, Jan 2012, doi: 10.1016/j.neulet.2011.10.074.
4. J. Rodriguez-López, "Identification of relevant hub genes for early intervention at gene co-expression modules with altered predicted expression in schizophrenia," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 98, no. Query date: 2022-10-13 15:16:28, 2020, doi: 10.1016/j.pnpbp.2019.109815.
5. E. Scarr, J. Y. Um, T. F. Cowie, dan B. Dean, "Cholinergic muscarinic M4 receptor gene polymorphisms: A potential risk factor and pharmacogenomic marker for schizophrenia," *Schizophrenia Research*, vol. 146, no. 1–3, hlm. 279–284, Mei 2013, doi: 10.1016/j.schres.2013.01.023.
6. A. D. Rosa, "Abnormal RasGRP1 Expression in the Post-Mortem Brain and Blood Serum of Schizophrenia Patients," *Biomolecules*, vol. 12, no. 2, 2022, doi: 10.3390/biom12020328.
7. S. D. Jong, "Gene-set analysis based on the pharmacological profiles of drugs to identify repurposing opportunities in schizophrenia," *Journal of Psychopharmacology*, vol. 30, no. 8, hlm. 826–830, 2016, doi: 10.1177/0269881116653109.
8. T. Lencz, "Targeting the schizophrenia genome: A fast track strategy from GWAS to clinic," *Molecular Psychiatry*, vol. 20, no. 7, hlm. 820–826, 2015, doi: 10.1038/mp.2015.28.
9. S. M. Saini *dkk.*, "Meta-analysis supports GWAS-implicated link between GRM3 and schizophrenia risk," *Transl Psychiatry*, vol. 7, no. 8, hlm. e1196–e1196, Agu 2017, doi: 10.1038/tp.2017.172.
10. S. G. Lago dan S. Bahn, "The druggable schizophrenia genome: from repurposing opportunities to unexplored drug targets," *npj Genom. Med.*, vol. 7, no. 1, hlm. 25, Mar 2022, doi: 10.1038/s41525-022-00290-4.
11. S. de Jong, L. R. Vidler, Y. Mokrab, D. A. Collier, dan G. Breen, "Gene-set analysis based on the pharmacological profiles of drugs to identify repurposing opportunities in schizophrenia," *J Psychopharmacol*, vol. 30, no. 8, hlm. 826–830, Agu 2016, doi: 10.1177/0269881116653109.
12. H. A. Gaspar dan G. Breen, "Drug enrichment and discovery from schizophrenia genome-wide association results: an analysis and visualisation approach," *Sci Rep*, vol. 7, no. 1, hlm. 12460, Des 2017, doi: 10.1038/s41598-017-12325-3.
13. H. A. Gaspar, "Drug enrichment and discovery from schizophrenia genome-wide association results: An analysis and visualisation approach," *Scientific Reports*, vol. 7, no. 1, 2017, doi: 10.1038/s41598-017-12325-3.
14. A. Jajodia *dkk.*, "Methylation of HTR3A promoter variant alters binding of transcription factor CTCF," *RSC Advances*.
15. J. Jian *dkk.*, "Associations of serotonin receptor gene HTR3A, HTR3B, and HTR3A haplotypes with bipolar disorder in Chinese patients," *Genet. Mol. Res.*, vol. 15, no. 3, 2016, doi: 10.4238/gmr.15038671.

16. D. Z. Paderina *dkk.*, "Genetic Polymorphisms of 5-HT Receptors and Antipsychotic-Induced Metabolic Dysfunction in Patients with Schizophrenia," *JPM*, vol. 11, no. 3, hlm. 181, Mar 2021, doi: 10.3390/jpm11030181.
17. X. Zhang dan Y. Sun, "The Predictive Role of ADRA2A rs1800544 and HTR3B rs3758987 Polymorphisms in Motion Sickness Susceptibility," *IJERPH*, vol. 18, no. 24, hlm. 13163, Des 2021, doi: 10.3390/ijerph182413163.
18. F. Yin *dkk.*, "Polymorphisms in the 5-hydroxytryptamine receptor 3B gene are associated with heroin dependence in the Chinese Han population," *Neuroscience Letters*, vol. 635, hlm. 123–129, Des 2016, doi: 10.1016/j.neulet.2016.10.033.
19. S. Takemoto-Kimura *dkk.*, "Calmodulin kinases: essential regulators in health and disease," *J. Neurochem.*, vol. 141, no. 6, hlm. 808–818, Jun 2017, doi: 10.1111/jnc.14020.
20. F. Filice, L. Janickova, T. Henzi, A. Bilella, dan B. Schwaller, "The Parvalbumin Hypothesis of Autism Spectrum Disorder," *Front. Cell. Neurosci.*, vol. 14, hlm. 577525, Des 2020, doi: 10.3389/fncel.2020.577525.
21. M. Piechota *dkk.*, "Glucocorticoid-Regulated Kinase CAMKIγ in the Central Amygdala Controls Anxiety-like Behavior in Mice," *IJMS*, vol. 23, no. 20, hlm. 12328, Okt 2022, doi: 10.3390/ijms232012328.
22. X. Luo *dkk.*, "Convergent lines of evidence support CAMKK2 as a schizophrenia susceptibility gene," *Mol Psychiatry*, vol. 19, no. 7, hlm. 774–783, Jul 2014, doi: 10.1038/mp.2013.103.
23. A. De Rosa *dkk.*, "Machine Learning algorithm unveils glutamatergic alterations in the post-mortem schizophrenia brain," *Schizophr*, vol. 8, no. 1, hlm. 8, Feb 2022, doi: 10.1038/s41537-022-00231-1.
24. A. Podder dan N. Latha, "New Insights into Schizophrenia Disease Genes Interactome in the Human Brain: Emerging Targets and Therapeutic Implications in the Postgenomics Era," *OMICS: A Journal of Integrative Biology*, vol. 18, no. 12, hlm. 754–766, Des 2014, doi: 10.1089/omi.2014.0082.
25. E. Walton *dkk.*, "Longitudinal epigenetic predictors of amygdala:hippocampus volume ratio," *J Child Psychol Psychiatr*, vol. 58, no. 12, hlm. 1341–1350, Des 2017, doi: 10.1111/jcpp.12740.
26. F. Rusconi, E. Battaglioli, dan M. Venturin, "Psychiatric Disorders and lncRNAs: A Synaptic Match," *IJMS*, vol. 21, no. 9, hlm. 3030, Apr 2020, doi: 10.3390/ijms21093030.
27. G. Barry *dkk.*, "The long non-coding RNA NEAT1 is responsive to neuronal activity and is associated with hyperexcitability states," *Sci Rep*, vol. 7, no. 1, hlm. 40127, Jan 2017, doi: 10.1038/srep40127.
28. S. Li *dkk.*, "Reduced Expression of Voltage-Gated Sodium Channel Beta 2 Restores Neuronal Injury and Improves Cognitive Dysfunction Induced by Aβ1-42," *Neural Plasticity*, vol. 2022, hlm. 1–21, Nov 2022, doi: 10.1155/2022/3995227.
29. D. Amar, M. E. Lindholm, J. Norrbom, M. T. Wheeler, M. A. Rivas, dan E. A. Ashley, "Time trajectories in the transcriptomic response to exercise - a meta-analysis," *Nat Commun*, vol. 12, no. 1, hlm. 3471, Jun 2021, doi: 10.1038/s41467-021-23579-x.
30. E. Rees *dkk.*, "Targeted Sequencing of 10,198 Samples Confirms Abnormalities in Neuronal Activity and Implicates Voltage-Gated Sodium Channels in Schizophrenia Pathogenesis," *Biological Psychiatry*, vol. 85, no. 7, hlm. 554–562, Apr 2019, doi: 10.1016/j.biopsych.2018.08.022.
31. S. Kyosseva, "The role of the extracellular signal-regulated kinase pathway in cerebellar abnormalities in schizophrenia," *The Cerebellum*, vol. 3, no. 2, hlm. 94–99, Jun 2004, doi: 10.1080/14734220410029164.

32. M. Hirayama-Kurogi *dkk.*, "Downregulation of GNA13-ERK network in prefrontal cortex of schizophrenia brain identified by combined focused and targeted quantitative proteomics," *Journal of Proteomics*, vol. 158, hlm. 31–42, Mar 2017, doi: 10.1016/j.jprot.2017.02.009.
33. B. K. Gorentla, C.-K. Wan, dan X.-P. Zhong, "Negative regulation of mTOR activation by diacylglycerol kinases," *Blood*, vol. 117, no. 15, hlm. 4022–4031, Apr 2011, doi: 10.1182/blood-2010-08-300731.
34. L. Ryskalin, F. Limanaqi, A. Frati, C. Busceti, dan F. Fornai, "mTOR-Related Brain Dysfunctions in Neuropsychiatric Disorders," *IJMS*, vol. 19, no. 8, hlm. 2226, Jul 2018, doi: 10.3390/ijms19082226.
35. K. J. Billingsley *dkk.*, "Regulatory characterisation of the schizophrenia-associated CACNA1C proximal promoter and the potential role for the transcription factor EZH2 in schizophrenia aetiology," *Schizophrenia Research*, vol. 199, hlm. 168–175, Sep 2018, doi: 10.1016/j.schres.2018.02.036.
36. D. Zhu *dkk.*, "CACNA1C (rs1006737) may be a susceptibility gene for schizophrenia: An updated meta-analysis," *Brain Behav*, vol. 9, no. 6, Jun 2019, doi: 10.1002/brb3.1292.
37. [37] N. Eckart *dkk.*, "Functional Characterization of Schizophrenia-Associated Variation in CACNA1C," *PLoS ONE*, vol. 11, no. 6, hlm. e0157086, Jun 2016, doi: 10.1371/journal.pone.0157086.
38. D. Baez-Nieto *dkk.*, "Analysing an allelic series of rare missense variants of *CACNA1I* in a Swedish schizophrenia cohort," *Brain*, vol. 145, no. 5, hlm. 1839–1853, Jun 2022, doi: 10.1093/brain/awab443.
39. A. Andrade, J. Hope, A. Allen, V. Yorgan, D. Lipscombe, dan J. Q. Pan, "A rare schizophrenia risk variant of CACNA1I disrupts CaV3.3 channel activity," *Sci Rep*, vol. 6, no. 1, hlm. 34233, Okt 2016, doi: 10.1038/srep34233.
40. Y. Xie, D. Huang, L. Wei, dan X.-J. Luo, "Further evidence for the genetic association between CACNA1I and schizophrenia," *Hereditas*, vol. 155, no. 1, hlm. 16, Des 2018, doi: 10.1186/s41065-017-0054-0.
41. T. Zhang *dkk.*, "Voltage-gated calcium channel activity and complex related genes and schizophrenia: A systematic investigation based on Han Chinese population," *Journal of Psychiatric Research*, vol. 106, hlm. 99–105, Nov 2018, doi: 10.1016/j.jpsychires.2018.09.020.
42. Multicenter Genetic Studies of Schizophrenia Consortium *dkk.*, "Genome-wide association analysis identifies 13 new risk loci for schizophrenia," *Nat Genet*, vol. 45, no. 10, hlm. 1150–1159, Okt 2013, doi: 10.1038/ng.2742.
43. D. Juraeva *dkk.*, "Integrated Pathway-Based Approach Identifies Association between Genomic Regions at CTCF and CACNB2 and Schizophrenia," *PLoS Genet*, vol. 10, no. 6, hlm. e1004345, Jun 2014, doi: 10.1371/journal.pgen.1004345.
44. A. Gibbons dan B. Dean, "The Cholinergic System: An Emerging Drug Target for Schizophrenia," *CPD*, vol. 22, no. 14, hlm. 2124–2133, Apr 2016, doi: 10.2174/1381612822666160127114010.
45. E. Scarr, J. Y. Um, T. F. Cowie, dan B. Dean, "Cholinergic muscarinic M4 receptor gene polymorphisms: A potential risk factor and pharmacogenomic marker for schizophrenia," *Schizophrenia Research*, vol. 146, no. 1–3, hlm. 279–284, Mei 2013, doi: 10.1016/j.schres.2013.01.023.
46. I. V. Pozhidaev *dkk.*, "Association of Cholinergic Muscarinic M4 Receptor Gene Polymorphism with Schizophrenia," *TACG*, vol. Volume 13, hlm. 97–105, Apr 2020, doi: 10.2147/TACG.S247174.

47. G. Lassi *dkk.*, "The CHRNA5–A3–B4 Gene Cluster and Smoking: From Discovery to Therapeutics," *Trends in Neurosciences*, vol. 39, no. 12, hlm. 851–861, Des 2016, doi: 10.1016/j.tins.2016.10.005.
48. K. Ohi *dkk.*, "Genome-Wide Variants Shared Between Smoking Quantity and Schizophrenia on 15q25 Are Associated With CHRNA5 Expression in the Brain," *Schizophrenia Bulletin*, vol. 45, no. 4, hlm. 813–823, Jun 2019, doi: 10.1093/schbul/sby093.
49. M. P. Forrest, M. J. Hill, D. H. Kavanagh, K. E. Tansey, A. J. Waite, dan D. J. Blake, "The Psychiatric Risk Gene Transcription Factor 4 (TCF4) Regulates Neurodevelopmental Pathways Associated With Schizophrenia, Autism, and Intellectual Disability," *Schizophrenia Bulletin*, vol. 44, no. 5, hlm. 1100–1110, Agu 2018, doi: 10.1093/schbul/sbx164.
50. C. Barkus, D. J. Sanderson, J. N. P. Rawlins, M. E. Walton, P. J. Harrison, dan D. M. Bannerman, "What causes aberrant salience in schizophrenia? A role for impaired short-term habituation and the GRIA1 (GluA1) AMPA receptor subunit," *Mol Psychiatry*, vol. 19, no. 10, hlm. 1060–1070, Okt 2014, doi: 10.1038/mp.2014.91.
51. A. M. Bygrave *dkk.*, "Hippocampal–prefrontal coherence mediates working memory and selective attention at distinct frequency bands and provides a causal link between schizophrenia and its risk gene GRIA1," *Transl Psychiatry*, vol. 9, no. 1, hlm. 142, Apr 2019, doi: 10.1038/s41398-019-0471-0.
52. C. Crisafulli *dkk.*, "Influence of GRIA1, GRIA2 and GRIA4 polymorphisms on diagnosis and response to antipsychotic treatment in patients with schizophrenia," *Neuroscience Letters*, vol. 506, no. 1, hlm. 170–174, Jan 2012, doi: 10.1016/j.neulet.2011.10.074.
53. L. E. Herzog *dkk.*, "Mouse mutants in schizophrenia risk genes *GRIN2A* and *AKAP11* show EEG abnormalities in common with schizophrenia patients," Neuroscience, preprint, Apr 2022. doi: 10.1101/2022.04.05.487037.
54. E. G. Poltavskaya *dkk.*, "Study of Early Onset Schizophrenia: Associations of GRIN2A and GRIN2B Polymorphisms," *Life*, vol. 11, no. 10, hlm. 997, Sep 2021, doi: 10.3390/life11100997.
55. R. Liu, W. Dang, Y. Du, Q. Zhou, Z. Liu, dan K. Jiao, "Correlation of functional GRIN2A gene promoter polymorphisms with schizophrenia and serum d-serine levels," *Gene*, vol. 568, no. 1, hlm. 25–30, Agu 2015, doi: 10.1016/j.gene.2015.05.011.
56. S. M. Saini *dkk.*, "Meta-analysis supports GWAS-implicated link between GRM3 and schizophrenia risk," *Transl Psychiatry*, vol. 7, no. 8, hlm. e1196–e1196, Agu 2017, doi: 10.1038/tp.2017.172.
57. N. L. O'Brien *dkk.*, "The functional GRM3 Kozak sequence variant rs148754219 affects the risk of schizophrenia and alcohol dependence as well as bipolar disorder," *Psychiatric Genetics*, vol. 24, no. 6, hlm. 277–278, Des 2014, doi: 10.1097/YPG.0000000000000050.
58. J. Mounce, L. Luo, A. Caprihan, J. Liu, N. I. Perrone-Bizzozero, dan V. D. Calhoun, "Association of GRM3 polymorphism with white matter integrity in schizophrenia," *Schizophrenia Research*, vol. 155, no. 1–3, hlm. 8–14, Mei 2014, doi: 10.1016/j.schres.2014.03.003.