Genetic Architecture of Schizophrenia: From Common Variants to Rare Mutations and Clinical Translation

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ABSTRACT

Schizophrenia is a prevalent mental illness that has a significant genetic component. Significant advancements have been made in recent research using modern genomic techniques on large samples to identify DNA variants linked to the condition and elucidate its underlying genetic architecture. It is now known that the genetic susceptibility to schizophrenia is polygenic, with risk alleles found in numerous genes along the entire allelic frequency spectrum. Additionally, it has been shown that additional neuropsychiatric phenotypes such as bipolar disorder, major depressive disorder, autistic spectrum disorder, intellectual disability, and attention-deficit hyperactivity disorder share risk genes with schizophrenia. These risk variations combine to form many sets of functionally connected genes, offering fresh perspectives on disease pathophysiology and opportunities for therapeutic research. The last 3 years have seen the most fascinating and important advances in understanding the causes of schizophrenia. Progress has been made in several areas, most notably the molecular genetics of this intricate mental and brain illness. However, there are still several crucial unanswered concerns that qualify the data's final clinical and scientific validity. However, it appears that not many people are aware of the recent advancements in this historically challenging field of study. This article's goal is to present a high-level overview of advancements, their constraints, and the consequences for clinical practice and research.

Keywords: Copy number variants, De novo mutations, Genome-wide association studies, Neurodevelopmental disorders, Polygenic risk score, Precision psychiatry, Psychiatric genetics, Psychiatric genomics, Rare variants, Schizophrenia, Single nucleotide polymorphisms, Synaptic plasticity.

Introduction

With a lifetime frequency of about 1%, schizophrenia is a crippling mental illness marked by hallucinations, delusions, thinking disorders, and cognitive deficiencies. Family, twin, and adoption studies provide evidence of a significant genetic contribution.[1] However, the disorder's pathophysiology and underlying causes are still unknown. Our understanding of genetic risk at the level of DNA variation has evolved significantly in recent years, mostly due to the use of cutting-edge genomic technologies on extremely large samples. There is proof that risk variations, many of which are linked to other neuropsychiatric conditions, exist throughout the whole allelic frequency spectrum. Furthermore, certain biological pathways have now been linked to the etiology of disease through genetic relationships involving various kinds of mutations.

The significance of schizophrenia for public health is evident. Schizophrenia's median lifetime prevalence is 0.7%–0.8%,[1] with a history of illness characterized by exacerbations, remissions, significant residual symptoms, and functional impairment.[2] Onset usually occurs between adolescence and early adulthood. Schizophrenia is the eighth leading cause of illness in the world, and morbidity is high.[3]

Furthermore, chemical use (mostly alcohol, nicotine, cannabis, and cocaine) and significant medical disorders (obesity, Type 2 diabetes mellitus) frequently coexist with schizophrenia.[4] People with schizophrenia are expected to live 15 years less than the general population, and there is a significant mortality rate from both natural and anthropogenic causes.[5] Schizophrenia has huge societal, familial, and personal costs.

Recent developments in schizophrenia genetics from de novo mutation and uncommon copy number variation investigations will be discussed in this review.

(CNV), minor insertion/deletion (indel) mutations, rare single nucleotide variants (SNV, defined as point mutations with a frequency less than 1%), and single nucleotide polymorphisms (SNPs, defined as point mutations with a frequency more than 1%)

Methods

This article was conducted as a narrative review informed by a structured literature-search strategy. The search process was designed to improve transparency and comprehensiveness but was not intended to fulfill all methodological requirements of a formal systematic review. Accordingly, no protocol registration was performed, no quantitative meta-analysis was undertaken, and risk-of-bias assessments were used to guide interpretation rather than study exclusion.

Studies were prioritized based on methodological rigor, sample size, replication status, and relevance to schizophrenia genetics and clinical translation. Large-scale consortia studies, including investigations from the Psychiatric Genomics Consortium (PGC), Schizophrenia Exome Sequencing Meta-analysis (SCHEMA), and cross-disorder psychiatric genomics initiatives, were preferentially included. Both primary research articles and high-impact review papers were evaluated.

Inclusion criteria comprised studies investigating common and rare genetic variation, functional genomics, neurodevelopmental mechanisms, polygenic risk prediction, pharmacogenomics, and translational applications in schizophrenia. Studies lacking adequate methodological detail, statistical robustness, or direct relevance to schizophrenia genetics were excluded. This review emphasizes replicated findings and emerging

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Short Title: Schizophrenia Genomics and Clinical Translation

integrative multi-omic approaches to provide an updated overview of schizophrenia genetic architecture.

Search Strategy and Evidence Evaluation

A detailed search strategy, including complete database-specific search strings and the final search date (March 31, 2026), is provided in Supplementary File S1. Study selection followed a structured screening process modeled on PRISMA principles (Supplementary Figure S1). Records were identified through PubMed, Scopus, and Web of Science; duplicates were removed, and titles, abstracts, and full texts were assessed for eligibility.

To enhance methodological transparency and reproducibility, complete database-specific search strategies for PubMed, Scopus, and Web of Science are provided in Supplementary File S1. The search was conducted through March 31, 2026. Study identification, screening, eligibility assessment, and final inclusion are summarized in Supplementary Figure S1, while the evidence appraisal framework used during synthesis is presented in Supplementary Table S1.

To improve interpretive rigor, evidence was weighted according to methodological quality, sample size, replication status, and study design. Large-scale meta-analyses, international consortia datasets (including PGC and SCHEMA), and independently replicated findings were assigned greater interpretive emphasis than candidate-gene studies or single-cohort investigations. Particular priority was given to findings supported across multiple genomic approaches (GWAS, exome sequencing, CNV analyses, transcriptomics, and functional studies), thereby increasing confidence in biological inference and clinical relevance.

The study identification, screening, eligibility assessment, and inclusion process are summarized in Supplementary Figure S1.

Etiological Indications

Numerous epidemiological studies have identified some risk factors of schizophrenia. Figure 1 summarizes a portion of this effort. A first-degree relative with schizophrenia has an odds ratio of nearly ten out of a wide range of prenatal and antenatal risk variables.[6] While the overall effects of some of the risk factors shown in Figure 1 are still unknown, there is evidence that biological sex, cannabis usage, urban living, and immigration status are risk factors for schizophrenia. The size of the odds ratio for family history indicates that looking for the familial determinants of schizophrenia is reasonable for etiological study, even when the attributable risk of some of these risk factors (such as place and season of birth) may be higher.[7]

Quality Appraisal

Although this study was conducted as a narrative review, methodological quality was considered during evidence synthesis. Greater interpretive weight was assigned to studies with large sample sizes, independent replication, rigorous statistical correction, consortium-scale datasets, and functional validation. Evidence from candidate-gene studies, small cohorts, and non-replicated findings was interpreted cautiously. Supplementary Table S1 summarizes the quality appraisal framework used to support the comparative evaluation of included studies.

This figure illustrates the major epidemiological risk factors associated with schizophrenia, including genetic predisposition, prenatal and perinatal complications, environmental exposures, early-life

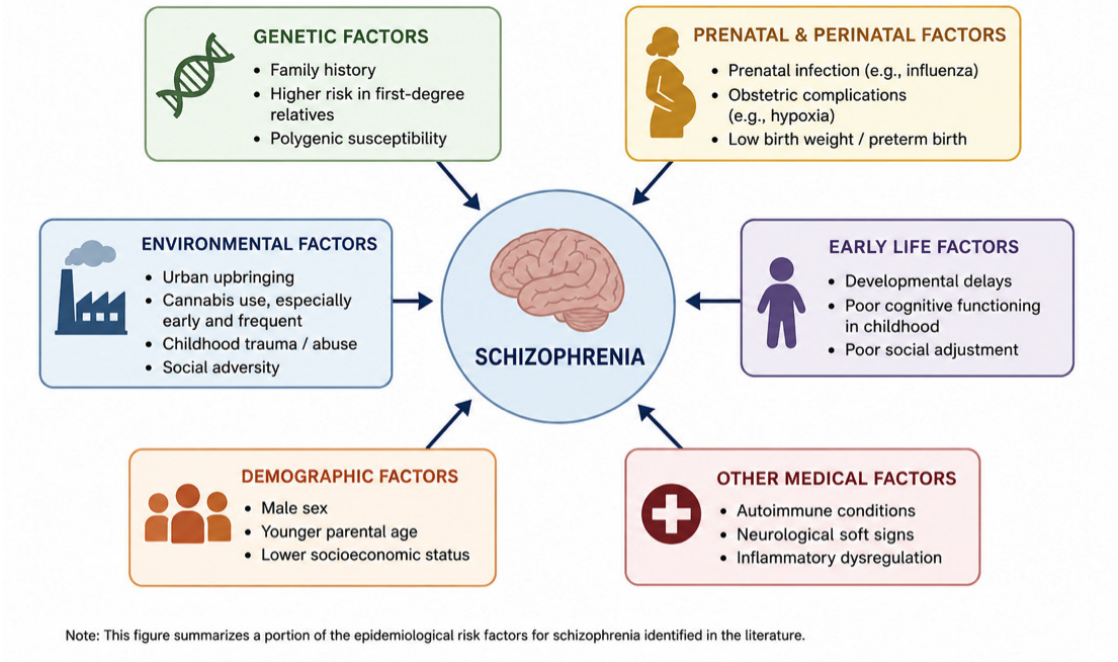

Fig 1 | Summary of selected epidemiological risk factors for schizophrenia

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developmental factors, demographic influences, and other medical conditions. These interconnected factors contribute to increased vulnerability and the multifactorial pathogenesis of schizophrenia. Examining the Family Background

The Risk Factor

Research on twins, adoptees, and families has been extensively employed in an effort to comprehend the relative contributions of environmental and genetic factors to schizophrenia risk.[8] These "old genetics" methods infer the functions of genes and environment indirectly through the phenotypic similarity of relatives. Genetic epidemiology investigations of schizophrenia have produced a very consistent set of findings, as shown in Table 1,[9,10] despite numerous significant assumptions and methodological problems with these studies.[8]

In a nutshell, schizophrenia is familial, meaning it "runs" in families. According to twin and adoption studies, the primary cause of schizophrenia's familiarity is genetics. Twin studies indicate the importance of little but significant shared environmental influences.

Table 1 | Genetic evidence in schizophrenia

Genetic evidence category		Key findings	Key data
Association studies		• Numerous candidate gene association studies with small samples. • *COMT* rs4680 most likely not associated. • Some neighboring markers/genes show suggestive associations in limited studies. • No "hard" replication.	Typical sample sizes: < 1,000 cases and controls per study.
De novo mutations	**De novo CNVs**	• Higher rate in cases vs controls. • Larger median size in cases. • Strong selection against pathogenic CNVs.	Rate in cases: 5% Rate in controls: 2% Median size >100 kb: Cases 574 kb vs Controls 337 kb Selection coefficient (s): 0.12 – 0.88 (s = 1 is lethal) Eliminated from population in < 5 generations
	Genes/Pathways enriched by de novo CNVs	• Enriched in post-synaptic density proteome. • Enrichment in genes in NMDAR and ARC complexes (synaptic plasticity).	
	De novo SNV/indels (exome sequencing)	• Overall exome-wide rate not higher than expected. • Enriched for loss-of-function (LoF) in cases without intellectual disability but low educational attainment. • Recurrent LoF mutations in *TAF13* and SETD1A. • Disrupted genes show higher connectivity in PPI networks. • Enrichment in pathways: ARC, NMDAR, FMRP targets, actin filament bundle assembly, chromatin remodeling/epigenetic regulation, genes also involved in ID/ASD.	No excess overall de novo SNV/indel rate. Enriched for LoF mutations.
Rare (uncommon) copy number variants (CNVs)		• Increased genome-wide burden of rare (<1%) CNVs; larger (>500 kb) deletions have greatest impact. • >15 loci associated (OR 2–60). • 10 recurrent CNVs remain significant after multiple testing (120 loci). • Enriched in pathways: NMDAR, mGluR5 (PSD), calcium channel signaling, FMRP targets, chromatin remodeling, immune signaling, miR-10a targets. • Many CNVs increase risk for other neuropsychiatric disorders (ASD, ID, epilepsy, ADHD).	Present in ~2.5% of patients overall. Individual frequency usually < 1 in 500. CNV sizes: typically >100 kb; large events >500 kb have greatest effect. OR range: 2 – 60
Rare inherited SNVs and indels		• Overall exome-wide burden not elevated. • Enrichment of rare disruptive variants in selected schizophrenia-relevant genes. • Enrichment in ARC, NMDAR, FMRP targets, and voltage-gated calcium channel genes. • Contribution of ultra-rare damaging alleles across many genes.	Exome sequencing samples: 2,536 cases and 2,543 controls. Significance threshold: MAF < 0.1%

CNV = copy number variant; SNV = single nucleotide variant; LoF = loss of function; NMDAR = N-methyl-D-aspartate receptor; ARC = activity-regulated cytoskeleton-associated protein; FMRP = fragile X mental retardation protein; PSD = post-synaptic density; OR = odds ratio; ID = intellectual disability; ASD = autism spectrum disorder; ADHD = attention-deficit/hyperactivity disorder; CM = congenital malformations; PPI = protein–protein interaction.

Box 1 | Historical contributions of linkage and candidate-gene studies

Prior to the GWAS era, linkage analyses and candidate-gene investigations provided important early evidence supporting a genetic basis for schizophrenia. Although many findings proved difficult to replicate due to limited statistical power, heterogeneous phenotypic definitions, and incomplete genomic coverage, these studies laid the foundation for contemporary psychiatric genomics. Modern large-scale GWAS, sequencing studies, and functional genomic approaches have largely superseded candidate-gene methodologies and now provide substantially stronger evidence for schizophrenia susceptibility loci and biological pathways.

Although linkage and candidate-gene studies provided important early evidence supporting genetic influences on schizophrenia, most reported associations have not remained significant under contemporary genome-wide significance thresholds. Modern GWAS, exome-sequencing, and functional-genomic approaches now provide substantially more robust and reproducible evidence regarding schizophrenia susceptibility genes and biological pathways.

Box 2 | Major advances in schizophrenia genomics since 2021

- Identification of 287 genome-wide significant schizophrenia loci through expanded Psychiatric Genomics Consortium (PGC) meta-analyses involving more than 320,000 participants.
- Fine-mapping analyses have prioritized genes involved in synaptic biology, neuronal differentiation, and cortical development.
- SCHEMA exome-sequencing studies identified rare coding variants in genes, including SETD1A, GRIN2A, CACNA1I, and TRIO, which confer substantial schizophrenia risk.
- Single-cell transcriptomic studies demonstrated enrichment of schizophrenia-associated variants in excitatory cortical neurons, interneurons, and developing neuronal progenitor populations.
- Cross-ancestry genomic investigations revealed broadly shared genetic architecture across populations while highlighting reduced portability of polygenic risk scores (PRS) outside European-ancestry cohorts.
- Integration of GWAS, transcriptomics, chromatin interaction mapping, and proteomics has improved functional interpretation of noncoding risk loci and facilitated prioritization of causal genes.

It most likely originated during pregnancy. Therefore, it is appropriate to think of schizophrenia as a complex feature that results from both environmental and genetic etiological influences. These findings are only vaguely instructive because they do not reveal the location of the genes or the nature of the environmental factors that either guard against or predispose to schizophrenia. Given the greater overall impact size and lower measurement error compared to standard evaluations of environmental effects, it makes sense to look for genetic influences that mediate vulnerability to schizophrenia. Keep in mind that a high heritability does not ensure that efforts to find candidate genes will be successful (Box 1).

Studies of Genome-Wide Linkage in Schizophrenia

Contemporary genotyping methods and Genetic loci linked to the etiology of numerous complex characteristics, including Type 2 diabetes mellitus, obesity, and Alzheimer's disease, have been found thanks to statistical analysis.[11] Figure 2 summarizes several "discovery science" methods that have been used to treat schizophrenia. The 27 samples displayed here comprised one to 294 multiplex pedigrees (see Glossary) with 32 to 669 (median 101) people with a restricted definition of schizophrenia (median 34). The first-stage genome scans contained 310–950 genetic markers (median 392). It is difficult to find "hard" replication, which is the implication of the same markers, alleles, and haplotypes in most samples (Box 2).

The lack of clear-cut or "hard" replication could be due to a number of factors. Concerning the teams that carried out this incredibly laborious research, it is probable that none of them had enough statistical power to identify the minor genetic alterations thought to be associated with schizophrenia.

For instance, to find a locus that accounts for ~5% of variance in schizophrenia liability at $\alpha = 0.001$, 4,900 pedigrees would need to have 80% power. Highly optimistic assumptions are made in these computations, and less favorable assumptions may result in sample size requirements greater than 50,000 sibling pairs. In contrast, Figure 2 shows fewer than 2,000 pedigrees overall.

Furthermore, etiological heterogeneity (various technological variations as well as combinations of genetic and environmental factors between samples, different ascertainment, assessment, genotyping, and statistical analysis between samples) contributed; their influence is unclear, but insufficient power is evident. If accurate, Figure 2 shows a combination of real and false positive results.

This figure synthesizes results from 27 genome-wide linkage scans conducted across multiplex pedigrees. Each horizontal panel represents an individual study, displaying multipoint logarithm of odds (LOD) scores across all chromosomes (1–22, X). Peaks indicate suggestive linkage signals (LOD ≥ 3.0), while the baseline reflects no linkage (LOD = 0).

All genomic coordinates, loci, effect-size estimates, and biological pathways shown are intended as conceptual summaries of published findings and should not be interpreted as original experimental results.

Across studies, sample sizes ranged from 1 to 294 pedigrees, with 32 to 669 individuals per study (median = 101), and 22 to 294 affected individuals with schizophrenia (median = 34). First-stage genome scans included 310–950 genetic markers (median = 392). The accompanying table summarizes key study characteristics, including the number of pedigrees, total individuals, affected cases, and marker density.

Despite multiple suggestive linkage peaks, there is limited evidence of consistent ("hard") replication across studies, defined as convergence on the same loci, alleles, or haplotypes. This inconsistency likely reflects limited statistical power, given that detection of loci explaining ~5% of variance would require substantially larger sample sizes (thousands of pedigrees), as well as etiological heterogeneity arising from differences in

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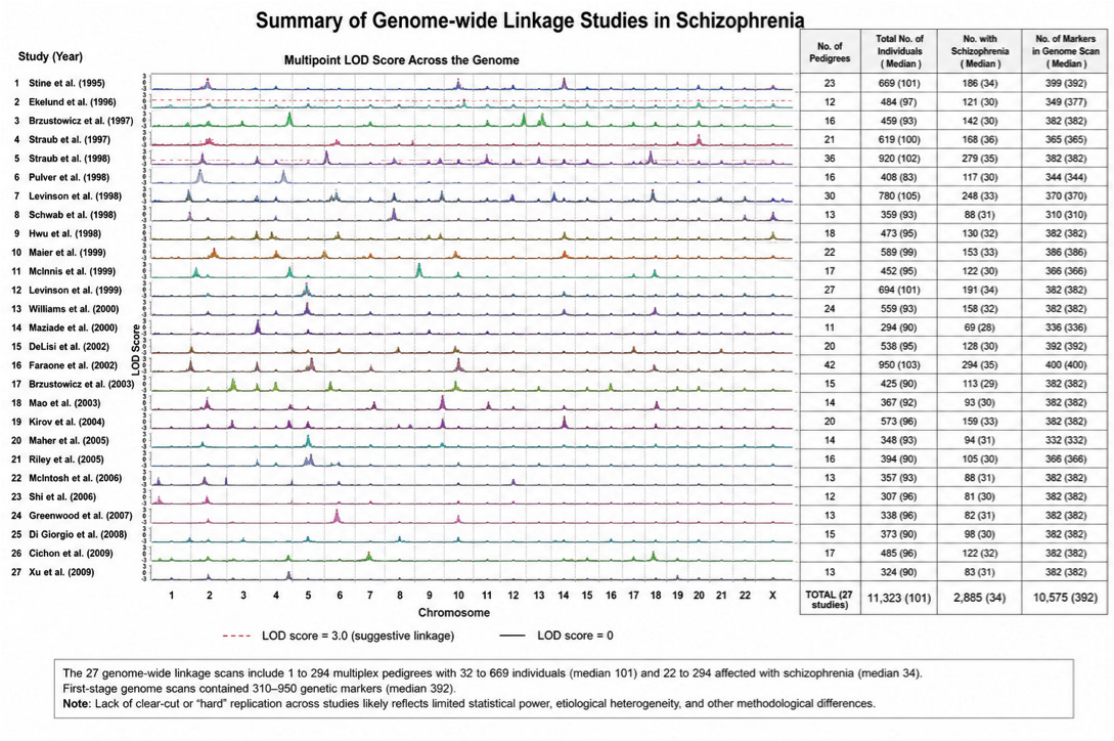

No. of Pedigrees	Total No. of Individuals (Median)	No. with Schizophrenia (Median)	No. of Markers in Genome Scan (Median)
23	669 (101)	186 (34)	399 (392)
12	484 (97)	121 (30)	349 (377)
16	459 (93)	142 (30)	382 (382)
21	619 (100)	168 (36)	365 (365)
36	920 (102)	279 (35)	382 (382)
16	408 (83)	117 (30)	344 (344)
30	780 (105)	248 (33)	370 (370)
13	359 (93)	88 (31)	310 (310)
18	473 (95)	130 (32)	382 (382)
22	589 (99)	153 (33)	386 (386)
17	452 (95)	122 (30)	366 (366)
27	694 (101)	191 (34)	382 (382)
24	559 (93)	158 (32)	382 (382)
11	294 (90)	69 (28)	336 (336)
20	538 (95)	128 (30)	392 (392)
42	950 (103)	294 (35)	400 (400)
15	425 (90)	113 (29)	382 (382)
14	367 (92)	93 (30)	382 (382)
20	573 (96)	159 (33)	382 (382)
14	348 (93)	94 (31)	332 (332)
16	394 (90)	105 (30)	366 (366)
13	357 (93)	88 (31)	382 (382)
12	307 (96)	81 (30)	382 (382)
13	338 (96)	82 (31)	382 (382)
15	373 (90)	98 (30)	382 (382)
17	485 (96)	122 (32)	382 (382)
13	324 (90)	83 (31)	382 (382)
TOTAL (27 studies)	11,323 (101)	2,885 (34)	10,575 (392)

Fig 2 | Summary of genome-wide linkage studies in schizophrenia

genetic background, environmental exposures, ascertainment strategies, phenotypic definitions, genotyping platforms, and analytical methods. Collectively, the observed linkage signals likely represent a mixture of true susceptibility loci and false-positive findings.

Association Research on Schizophrenia

Schizophrenia, like the majority of numerous genetic case-control association studies, has been conducted on complicated variables in biomedicine.[12] Small sample sizes and the propensity to genotype a single genetic marker out of the hundreds that may be accessible in a gene make it difficult to evaluate many studies, despite changes in research technique. For instance, a commonly researched functional genetic marker in COMT (rs4680) is most likely not linked to schizophrenia,[13] while neighboring genetic markers evaluated in a small number of studies might be.[14]

Nonetheless, some methodologically sound association studies of schizophrenia seem to suggest the involvement of multiple candidate genes in the etiology of schizophrenia, as will be covered in the following section. "Hard" replication is still elusive, much like the linkage study findings.

De Novo Mutations

A significant portion of the risk for schizophrenia may be inherited, according to high heritability estimates.[2] Nevertheless, alleles that are not inherited, such as newly emerging (de novo) mutations, have also been demonstrated to increase risk. Furthermore, a higher risk of schizophrenia has been linked to a higher paternal age at conception, which is correlated with the number of de novo mutations seen in a person.[15,16] Studies of CNVs provided the first molecular evidence linking de novo mutation to schizophrenia.[17,18] The CNV de novo mutation rate was shown to be significantly greater in individuals with schizophrenia (~5%) compared to controls (2%), with some evidence pointing to a higher prevalence among those without a family history of the condition.[17–19]

Additionally, compared to controls, the median size of de novo CNVs > 100 Kb in schizophrenia cases is greater (574 Kb[17,18]) (337 Kb[19]). For CNVs that are strongly linked to schizophrenia, selection coefficients (s) ranging from 0.12 to 0.88 have been calculated; a selection value of 1 indicates reproductive lethality.[12] De novo CNVs at loci linked to schizophrenia are eliminated from the population in fewer than five generations due to this level of selection.[12]

Researching gene sets that are overrepresented in schizophrenia and disrupted by de novo mutations has yielded new insights into the molecular mechanisms underlying the condition.

For instance, genes in the post-synaptic-density proteome are more likely to be affected by schizophrenia de novo CNVs.[17] Genes that encode components of the N-methyl-D-aspartate receptor (NMDAR) and neuronal activity-regulated cytoskeleton-associated protein (ARC) complexes are primarily responsible for this connection implicated in the plasticity of synapses.[6] Exome sequencing research has made it possible to assess de novo SNVs and indels in schizophrenia in more recent times. The exome-wide rate of de novo SNV/indel mutations is not higher in cases than the population expectation, in contrast to research on de novo CNVs in schizophrenia.[11] The largest investigation to

date[20] did not uncover these results, despite several smaller studies reporting somewhat higher rates of de novo SNVs and a higher fraction of de novo mutations occurring as nonsynonymous in schizophrenia compared with controls.[13–15] But de novo SNV/indel mutations that cause loss of function are enhanced among patients who did not have an intellectual handicap but had low educational attainment.[11]

De Novo Loss of Function in Multiple Cases of Schizophrenia

Two genes (TAF13, SETD1A) have been found to contain SNV/indel mutations,[21,22] indicating that they are probably related to the illness.

In schizophrenia, the products of genes disrupted by harmful de novo mutations exhibit higher connectedness in protein–protein interaction (PPI) networks than would be predicted by chance[14] or when compared to controls.[23] It has also been demonstrated that haploinsufficiency-prone genes are more likely to be disrupted by nonsense de novo mutations in schizophrenia,[23] indicating that a large number are probably harmful. Even while there isn't a higher exome-wide rate of de novo SNV/indel mutations,

These mutations are more common in instances of schizophrenia in previously linked groupings of biologically related genes. In particular, substantial enrichments in cases for nonsynonymous and loss-of-function de novo mutations have further implicated the ARC and NMDAR postsynaptic protein complexes, which have been linked to schizophrenia in investigations of de novo CNVs.[12] Significant enrichments of de novo SNV/indel mutations in schizophrenia have also been found in brain-expressed genes targeted by fragile X mental retardation protein (FMRP),[11] in line with a previous finding of a comparable enrichment for de novo mutations in ASD.[17] Additional sets that are enriched for de novo mutations include those associated with the assembly of actin filament bundles,[21] genes involved in chromatin-remodeling and other aspects of epigenetic control,[22,23] and genes affected by de novo mutations in intellectual disability (ID) and ASD.[24]

More recent large-scale sequencing efforts have strengthened evidence for rare protein-truncating variants contributing to schizophrenia susceptibility. SCHEMA analyses involving more than 120,000 exomes identified significant enrichment of rare damaging variants in genes involved in synaptic transmission, glutamatergic signaling, chromatin remodeling, and neuronal development. These findings provide convergent support for biological pathways previously implicated through GWAS and CNV studies while substantially improving confidence in individual susceptibility genes.

Uncommon Variations in Copy Numbers

Numerous repeatable relationships have recently been reported in studies of uncommon (<1%) CNVs in schizophrenia. It is believed that individuals suffering from schizophrenia have a markedly higher genome-wide burden of uncommon CNVs in comparison to controls, with big (>500 Kb) deletions typically showing the greatest impact.[12,18–20] Since the first CNV linked to schizophrenia was found to be a deletion at 22q11.2,[21,22] investigations of uncommon CNVs involving more than 20,000 cases have found links at more than 15 loci[20,23,24] (Figure 3). With odds ratios (OR) ranging from two to 60, most of these CNVs significantly raise the likelihood of developing schizophrenia.[24] Although they are present in about 2. ~5% of patients overall,[24] their individual contribution to the overall population variance in schizophrenia genetic liability is minimal because their frequency among patients is frequently less than one in 500.[25] The majority of CNVs linked to schizophrenia are big and recurrent, indicating that several mutation events have happened at the same or nearly identical genomic location.

Low copy repeats (LCRs), which drive mutation by nonallelic homologous recombination, are repeated genomic regions that typically surround the breakpoints of recurrent CNVs.[26] After adjusting for the multiple testing of 120 possible recurrent CNV loci in the human genome, 10 recurrent CNVs have been statistically linked to schizophrenia (Figure 3). Because many genes and regulatory elements are frequently disrupted, it is still difficult to derive biological insights from recurrent CNVs. However, schizophrenia has also been linked to single-gene disruptive non-recurrent CNVs in NRXN1, VIPR2, and PAK7.

Recent integrative analyses combining CNV data with transcriptomic and functional genomic resources have further demonstrated convergence between CNV-associated genes and pathways implicated by common variant studies. These investigations consistently highlight synaptic signaling, neuronal differentiation, calcium-channel activity, chromatin regulation, and cortical neurodevelopment as shared biological mechanisms underlying schizophrenia susceptibility.

Even if only the NRXN1 relationship survives correction for the numerous mutations, these mutations may provide more insight into the pathophysiology of the disease, testing of 20,000 human genes. Neurexin 1, a synaptic cell adhesion molecule that connects presynaptic and postsynaptic neurons, is encoded by NRXN1.[27]

Rare CNVs in schizophrenia are enriched in biological pathways previously linked to schizophrenia, including the NMDAR and metabotropic glutamate receptor 5 (mGluR5) components of the postsynaptic density (PSD), calcium channel signaling (see single nucleotide polymorphisms below), and FMRP targets.[20] Chromatin remodeling complexes, immune system signaling components, and microRNA miR-10a targets are other gene sets that have recently been linked to uncommon CNV research.[20]

It has been demonstrated that CNVs linked to schizophrenia raise the likelihood of developing other neuropsychiatric conditions.[28,29] For instance, ASD is also linked to duplications of the Williams-Beuren and Prader-Willi/Angelman syndrome areas associated with schizophrenia.[9,30]

15q11.2 and 15q13.3 deletions in epilepsy[31,32] and 16p13.11 duplications in ADHD.[33] Large cohorts of

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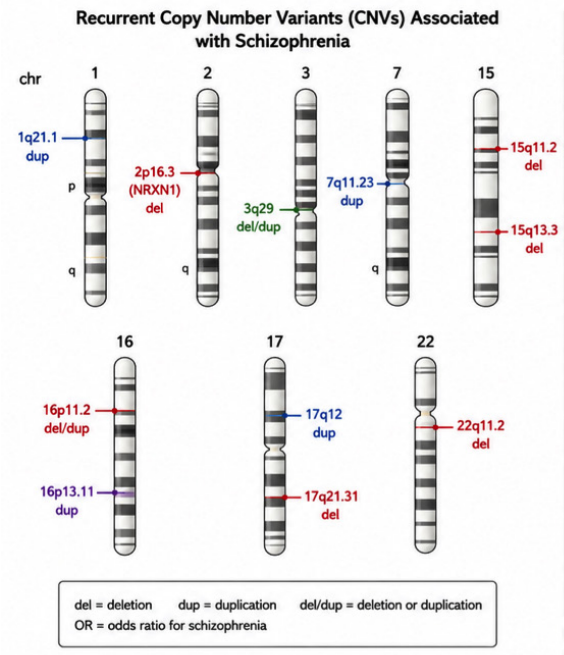
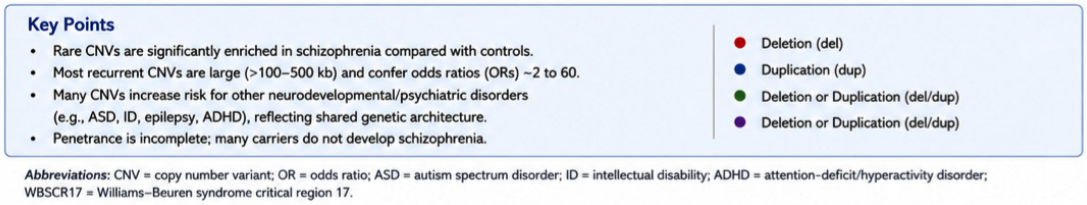


CNV (Locus)	Type	OR Range (approx.)	Penetrance (approx.)	Key Gene(s) / Region
1q21.1	Duplication	2 – 5	Low	Multiple genes
2p16.3 (NRXN1)	Deletion	2 – 6	Low	NRXN1
3q29	Deletion / Duplication	5 – 10	Low–Mod	NRROS, PAK2, others
7q11.23	Duplication	2 – 6	Low	WBSCR17
15q11.2	Deletion	2 – 10	Low	TUBGCP5, CYFIP1, NIPA1
15q13.3	Deletion	2 – 10	Low	CHRNA7, OTUD7A, others
16p11.2	Deletion / Duplication	5 – 20	Low–Mod	KCTD13, MAPK3, others
16p13.11	Duplication	2 – 8	Low	Multiple genes
17q12	Duplication	2 – 6	Low	KANSL1, MAPT, others
17q21.31	Deletion	2 – 6	Low	MAPT region
22q11.2	Deletion	10 – 60	Low–Mod	TBX1 and multiple genes

Note: All loci shown have been reported in ≥20,000 cases in one or more studies and replicated across independent datasets and consortia.



Abbreviations: CNV = copy number variant; OR = odds ratio; ASD = autism spectrum disorder; ID = intellectual disability; ADHD = attention-deficit/hyperactivity disorder; WBSCR17 = Williams–Beuren syndrome critical region 17.

Fig 3 | Recurrent copy number variants (CNVs) associated with schizophrenia. Schematic representation of recurrent schizophrenia-associated CNV loci mapped to their chromosomal locations, together with approximate odds ratios (ORs), penetrance estimates, and representative genes or genomic regions implicated in disease susceptibility. The figure highlights well-established CNVs identified through large-scale case–control and consortium-based studies, including 1q21.1 duplication, 2p16.3 (NRXN1) deletion, 3q29 deletion/duplication, 7q11.23 duplication, 15q11.2 deletion, 15q13.3 deletion, 16p11.2 deletion/duplication, 16p13.11 duplication, 17q12 duplication, 17q21.31 deletion, and 22q11.2 deletion. These structural variants typically exhibit larger effect sizes than common single-nucleotide variants but are less frequent in the population and display variable penetrance. Many CNVs confer risk across multiple neurodevelopmental and psychiatric disorders, supporting shared biological mechanisms involving synaptic function, neurodevelopment, and gene regulation. OR and penetrance values are approximate ranges compiled from published literature and are intended for comparative illustration only.
Abbreviations: CNV, copy number variant; del, deletion; dup, duplication; NRXN1, neurexin 1; OR, odds ratio.
Note: This figure is a conceptual synthesis based on published studies and does not represent original association data. Estimates are illustrative and should not be interpreted as precise clinical risk predictions

individuals with early-onset neurodevelopmental abnormalities, such as ID, ASD, and congenital malformations (CM), are enriched in up to 72 pathogenic CNVs, most of which are shown in Figure 2.[34,35] In contrast to schizophrenia, it has been proposed that people with several pathogenic CNVs are more likely to have an earlier-onset neurodevelopmental disease (ID/ASD/CM).[36] Reciprocal CNVs, or simultaneous deletions and duplications, can occasionally seem to have various consequences on phenotype. For instance, obesity and low body mass index are linked to deletions and duplications at 16p11.2, respectively.[37,38] While deletion of this locus is one of the biggest risk factors for schizophrenia, duplications at 22q11.2 are far less common in schizophrenia than in controls.[39,40]

For schizophrenia and other neurodevelopmental disorders, the CNVs in Figure 2 are thought to have relatively high, but incomplete, penetrance; the majority have lower penetrance for schizophrenia than for the other illnesses.[28] However, a recent major investigation that demonstrated the degree of cognitive performance in these CNVs has called into doubt their incomplete penetrance.[41]

Non-affected carriers of CNVs linked to schizophrenia are found to be between those seen in community controls and schizophrenia patients.[42]

Insertion/Deletion Mutations and Uncommon Single-Nucleotide Variations

In recent years, many studies have examined rare inherited (as opposed to de novo) alleles in schizophrenia using modern sequencing techniques. Some studies have found intriguing results,[43,44] but because of their limited sample size, the results are still mostly

ambiguous. Exome sequencing in big samples (2536 patients and 2543 controls) has only been used in one study on schizophrenia yet.[45] Overall, the exome-wide burden of rare variation was not elevated in cases, and no single rare variant (MAF < 0.1%) was linked at genome-wide significance. Nonetheless, a markedly elevated burden of uncommon, disruptive alleles was found in a group of 2546 genes chosen for their increased likelihood of being linked to schizophrenia. Numerous genes shared this burden. Significant enrichments for rare disruptive SNVs and indels were discovered in proteins connected to ARC and NMDAR genes, FMRP targets, and voltage-gated calcium channels, just as in the de novo CNV and SNV investigations.[45] Although bigger samples are needed to establish strong correlations with particular genes or alleles, this work shows a contribution of ultra-rare harmful alleles dispersed across numerous genes in schizophrenia.

Overview of association studies, de novo mutations, and rare variants. Findings highlight limited replication in association studies, increased burden of de novo CNVs (larger and more frequent in cases), pathway enrichment (NMDAR, ARC, FMRP), and contribution of rare disruptive variants across multiple genes.

Polymorphisms of a Single Nucleotide

Genome-wide association studies (GWAS) have transformed understanding of schizophrenia genetics by demonstrating that disease susceptibility is highly polygenic and influenced by thousands of common variants of individually small effect. Early GWAS identified a limited number of loci, including associations reported by O'Donovan et al. (2008)[46] and Ripke et al. (2013).[47] Subsequent Psychiatric Genomics Consortium (PGC) meta-analyses dramatically increased statistical power, leading to the landmark identification of 108 genome-wide significant loci in approximately 36,989 cases and 113,075 controls. More recent large-scale analyses expanded this number to 287 independent loci and implicated genes involved in synaptic organization, neuronal signaling, chromatin regulation, and neurodevelopment.[46–50]

The first large Psychiatric Genomics Consortium (PGC) schizophrenia GWAS identified 108 genome-wide significant loci in approximately 37,000 cases and 113,000 controls. Subsequent meta-analyses substantially expanded these discoveries. The largest current consortium analysis reported 287 independent schizophrenia-associated loci and prioritized genes involved in synaptic organization, neuronal signaling, chromatin regulation, and neurodevelopment. Throughout this review, the 108-locus result is referenced as the landmark 2014 PGC discovery, whereas the 287 loci represent the current estimate from the large-scale consortium.

Genes that have long been thought to be important in schizophrenia, including the dopamine receptor D2 gene, which codes for the therapeutic target of the majority of antipsychotic medications, have additional genome-wide significant relationships.[51–54] This implies that novel common allele connections may provide biological insights that could lead to the discovery of new therapeutic targets. After adjusting for multiple testing, gene-set studies have not yet revealed any biological pathway that is significantly enriched for the 128 genome-wide significant associations for schizophrenia; a conclusive investigation is still pending.[51] Nonetheless, the correlations are stronger for enhancers expressed in the brain as well as for enhancers in immune-related tissues.[51]

Common risk alleles have been found by combining GWAS data from BD and schizophrenia,[46,55] while polygenic risk. Additionally, some risk genes may have more particular impacts at the level of the mental phenotype, since scores have been able to partially differentiate between various diseases.[46] Lower cognitive capacity has also been demonstrated to be predicted by schizophrenia polygenic risk scores,[47] indicating that these alleles may be involved in the cognitive impairments linked to the condition (Tables 2, 3).

Genome-wide association studies (GWAS) of schizophrenia illustrate the polygenic architecture of the disorder (Figure 4). The Manhattan plot displays SNP associations across all chromosomes, with the genome-wide significance threshold indicated ($P < 5 \times 10^{-8}$). Multiple

Table 2 | Summary of GWAS findings and common SNPs in schizophrenia

Feature	Key Findings	Quantitative Details
Common SNP associations	Numerous risk alleles identified; individually, small effects	ODDS RATIOS (ORS) ‹ 1.2
Polygenic architecture	Schizophrenia influenced by many common variants	›1,000 alleles contribute
Heritability explained	Common variants account for substantial genetic liability	~30%–50%
GWAS significance threshold	A stringent statistical cutoff is required	$P ‹ 5 \times 10^{-8}$
PGC findings (2014)	Initial landmark GWAS	108 loci
PGC findings (2022)	Expanded consortium meta-analysis	287 loci
Key genomic region	Strongest association in the MHC region	Chr6p21 (~8 Mb, high LD)
Candidate genes	Includes biologically relevant targets	*DRD2* (dopamine receptor)
Functional enrichment	Signals enriched in regulatory regions	Brain enhancers, immune tissues
Cross-disorder overlap	Shared genetic risk with other disorders	Bipolar disorder (BD)
Polygenic risk scores (PRS)	Predict disease risk and traits	Associated with cognitive impairment

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Table 3 | Landmark schizophrenia genomic studies since 2016

Study	Sample Size	Major Finding	Key Effect
Sekar et al. (2016)[56]	~65,000	C4 structural variation	Synaptic pruning mechanism
PGC Schizophrenia Working Group (2018)	>100,000	Expanded GWAS loci	Polygenic architecture
Bryois et al. (2022)[57]	>1 million cells	Cell-type enrichment	Excitatory neurons implicated
Trubetskoy et al. (2022)[58]	>320,000 individuals	287 risk loci	Synaptic biology prioritization
Singh et al. (2022) (SCHEMA)[59]	>120,000 exomes	Rare coding variants	SETD1A, GRIN2A, CACNA1G
Recent cross-ancestry studies (2023–2025)	Multi-ancestry cohorts	PRS transferability	Improved risk prediction equity

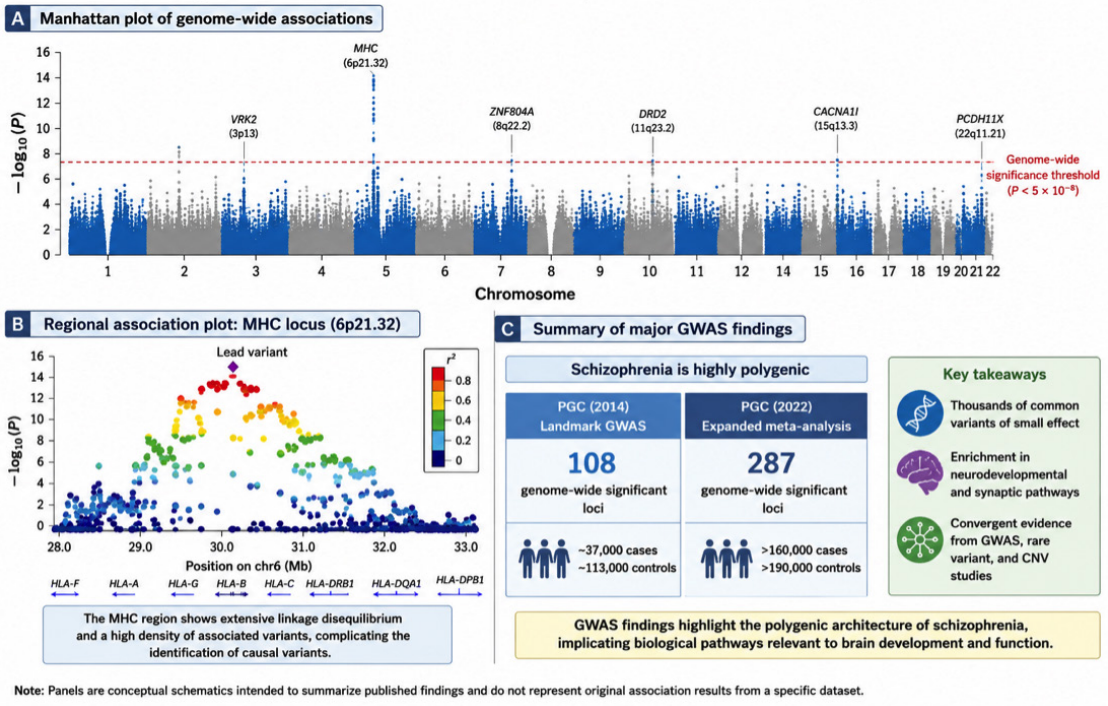

Fig 4 | Genome-wide association study (GWAS) findings in schizophrenia. (A) Conceptual Manhattan plot illustrating genome-wide significant associations across the genome and the conventional significance threshold ($P < 5 \times 10^{-8}$). (B) Conceptual regional association plot of the major histocompatibility complex (MHC) locus highlighting extensive linkage disequilibrium and challenges in causal variant identification. (C) Summary of major GWAS findings. The landmark 2014 PGC analysis identified 108 loci, whereas subsequent consortium-based meta-analyses expanded the number of genome-wide significant loci to 287. Collectively, schizophrenia demonstrates a highly polygenic architecture involving thousands of common variants of small effect that converge on neurodevelopmental and synaptic pathways.[46,47]
Note: Panels are conceptual schematics intended to summarize published findings and do not represent original association results generated from a specific dataset

Table 4 | Variant classes alignment with effect size, frequency, and examples

Variant Class	Representative Genes/Loci	Approximate Frequency	Typical Effect Size
Common SNPs	DRD2, CACNA1C, MHC/C4	>1%	OR 1.02–1.20
Rare coding variants	SETD1A, GRIN2A, TRIO, CACNA1G	<0.1%	OR 2–20+
CNVs	22q11.2, 1q21.1, NRXN1	<0.5%	OR 2–60
De novo mutations	SETD1A, TAF13	Very rare	High individual risk
Polygenic burden	Thousands of loci	Common	PRS explains ~7%–10% liability variance

loci surpass this threshold, including a prominent signal in the major histocompatibility complex (MHC) region on chromosome 6. Despite the identification of 128 independent significant associations across 108 loci, individual variants confer small effect sizes (ODDS RATIOS (ORS) < 1.2) (Table 4). Figure 5 highlights the cumulative contribution of numerous common alleles and enrichment of signals in brain and immune-related regulatory regions, supporting a highly polygenic and biologically complex etiology.

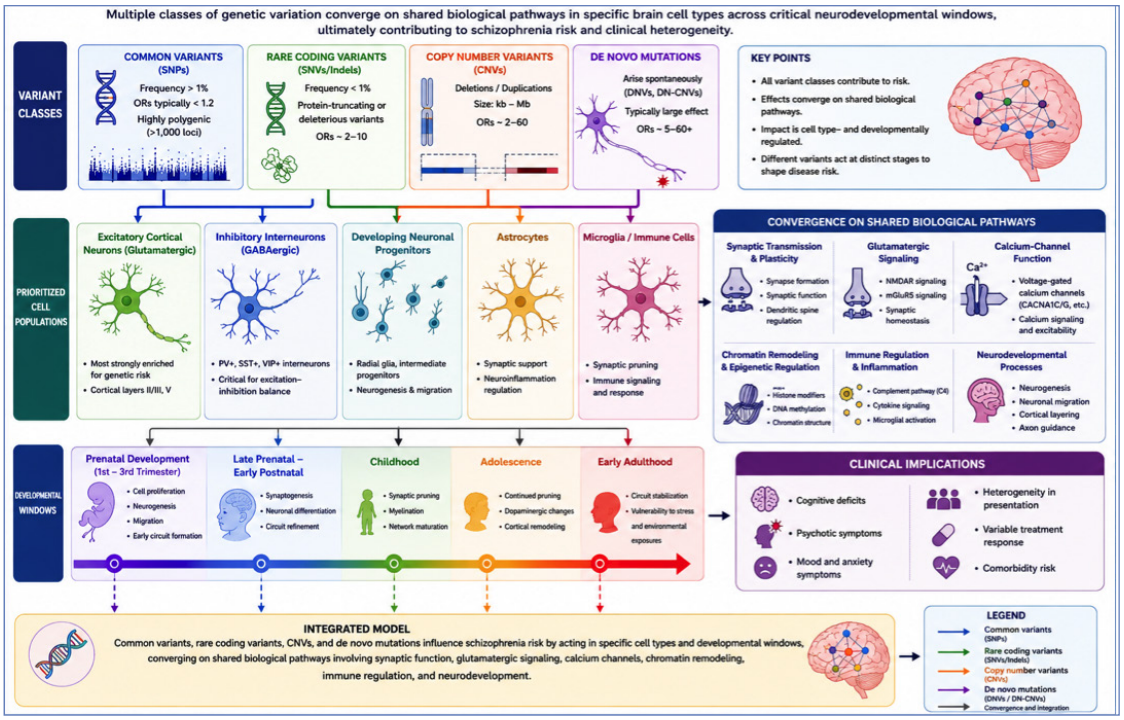

Fig 5 | Integrated model of schizophrenia genetic architecture across developmental and cellular contexts

The figure summarizes how common variants, rare coding variants, copy number variants (CNVs), and de novo mutations converge on shared biological pathways. Genetic risk is mapped onto prioritized cell populations, including excitatory cortical neurons, inhibitory interneurons, and developing neuronal progenitors, and linked to key pathways involving synaptic transmission, glutamatergic signaling, calcium-channel function, chromatin remodeling, immune regulation, and neurodevelopment. Developmental windows spanning prenatal brain development through adolescence are highlighted to illustrate the temporal framework through which genetic susceptibility influences disease risk.

Recent Advances in Schizophrenia Genomics

Fine-Mapping of the MHC Region and Complement Component 4 (C4)

One of the most important advances in schizophrenia genetics has been the fine-mapping of the major histocompatibility complex (MHC) locus on chromosome 6. Although early GWAS consistently identified the MHC region as the strongest common variant association signal, the extensive linkage disequilibrium across this locus initially hindered identification of causal genes. Subsequent work demonstrated that structural variation affecting complement component 4 (C4), particularly increased C4A expression, contributes substantially to schizophrenia risk through excessive synaptic pruning during neurodevelopment. These findings provided a mechanistic bridge between immune signaling, synaptic refinement, and schizophrenia pathophysiology.

Expanded GWAS and Polygenic Architecture

Recent Psychiatric Genomics Consortium (PGC) studies involving hundreds of thousands of participants have substantially expanded the number of genome-wide significant schizophrenia loci beyond the original 108 loci. These studies further confirmed the highly polygenic nature of schizophrenia, with thousands of common alleles collectively contributing to disease liability. Functional enrichment analyses consistently implicate synaptic signaling, neuronal differentiation, calcium-channel pathways, chromatin remodeling, and excitatory neuronal networks.

Large-Scale Exome Sequencing and Rare Coding Variants

Large exome sequencing studies, particularly those conducted by the Schizophrenia Exome Meta-Analysis (SCHEMA) consortium, have identified rare protein-truncating variants with substantial effects on schizophrenia risk. Genes including SETD1A, GRIN2A, CACNA1G, and TRIO have emerged as robust susceptibility loci. These discoveries reinforce convergence onto synaptic, glutamatergic, and neurodevelopmental pathways previously implicated by GWAS and CNV analyses.

Cross-Ancestry and Population Diversity Studies

Recent cross-ancestry investigations have demonstrated that schizophrenia genetic architecture is broadly shared across populations, although allele frequencies, linkage disequilibrium patterns, and predictive performance of polygenic risk scores vary substantially between ancestral groups. The historical overrepresentation of European ancestry cohorts remains a major limitation in psychiatric genomics. Expanding genetic

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studies to African, Asian, Latin American, and other underrepresented populations is critical for improving biological insight, risk prediction accuracy, and equitable clinical translation.

Several studies have demonstrated reduced portability of schizophrenia polygenic risk scores when models trained predominantly in European populations are applied to African, South Asian, East Asian, or admixed populations.[47,50] Differences in allele frequencies, linkage disequilibrium structure, environmental exposures, and reference panel representation contribute to reduced calibration and predictive accuracy. Best practices for equitable implementation include increasing representation of diverse ancestral groups in discovery cohorts, developing ancestry-aware prediction models, conducting external validation across populations, reporting calibration metrics alongside discrimination measures, and ensuring transparent communication of uncertainty in clinical settings.

Several studies have demonstrated that schizophrenia PRS developed in European-ancestry cohorts may lose 50%–80% of their predictive performance when applied to African-ancestry populations, with intermediate reductions observed in South Asian, East Asian, and admixed cohorts. These findings emphasize the need for ancestry-diverse discovery datasets, population-specific calibration procedures, and reporting of both discrimination (AUC) and calibration metrics when evaluating clinical performance.

Polygenic risk scores trained predominantly in European-ancestry cohorts exhibit substantially reduced predictive performance when applied to non-European populations. Several studies have reported losses of approximately 50%–80% in predictive accuracy in African-ancestry cohorts, with intermediate reductions observed in South Asian, East Asian, and admixed populations. These reductions arise from differences in linkage disequilibrium structure, allele frequencies, environmental exposures, and reference-panel representation. Consequently, both discrimination metrics (e.g., AUC) and calibration metrics should be reported when evaluating PRS performance across ancestries.[60,61]

Single-Cell and Multi-Omic Functional Integration

Advances in single-cell transcriptomics, epigenomics, chromatin accessibility mapping, and spatial transcriptomics have improved understanding of how schizophrenia-associated variants influence specific brain cell populations. Risk loci are strongly enriched in excitatory cortical neurons, interneurons, and developing neuronal populations of the prefrontal cortex and hippocampus. Integrative multi-omic approaches combining GWAS, transcriptomics, chromatin interaction data, and proteomics are increasingly enabling functional prioritization of causal genes and regulatory elements underlying schizophrenia susceptibility.

Recent Advances in Schizophrenia Genomics

Recent years have witnessed major advances in schizophrenia genetics, including the expansion of GWAS discoveries from 108 to 287 risk loci, identification of rare coding variants through SCHEMA exome sequencing, improved fine-mapping of the major histocompatibility complex (MHC) region, integration of single-cell transcriptomics with genetic association data, and increased recognition of ancestry-specific limitations in polygenic risk score portability. Collectively, these developments have strengthened the understanding of schizophrenia as a neurodevelopmental disorder involving convergent genetic mechanisms across common, rare, and structural variants.

Clinical Translation: Polygenic Risk Scores, Pharmacogenomics, and Precision Psychiatry

Polygenic Risk Scores and Predictive Psychiatry

Polygenic risk scores (PRS) aggregate the effects of thousands of common genetic variants into a quantitative estimate of inherited susceptibility. In schizophrenia, PRS has demonstrated utility in stratifying relative genetic risk and identifying associations with cognitive deficits, age at onset, symptom dimensions, and disease chronicity. Nevertheless, current predictive performance remains insufficient for standalone clinical diagnosis due to moderate discriminative accuracy and substantial overlap between cases and controls.[50]

The clinical utility of PRS may improve when integrated with environmental exposures, neurodevelopmental history, neuroimaging biomarkers, cognitive assessments, and digital phenotyping approaches. Importantly, PRS models currently show reduced portability across ancestries because most discovery datasets are heavily enriched for European populations. Addressing ancestry bias and improving calibration across diverse populations remain essential prerequisites for equitable clinical implementation.

Liability-scale SNP heritability estimates derived from large European-ancestry GWAS generally range from approximately 20%–30%, indicating that common variants explain a substantial proportion of schizophrenia genetic liability. Current PRS models explain approximately 7%–10% of liability variance depending on discovery sample size, ancestry composition, and statistical methodology.

Individuals within the highest schizophrenia polygenic-risk-score decile generally demonstrate approximately three- to eightfold greater relative risk compared with individuals in the lowest decile, although estimates vary according to ancestry, cohort composition, and PRS construction methodology.[61,62] Predictive performance remains moderate, with area-under-the-curve (AUC) values generally ranging from 0.65 to 0.75 in European-ancestry cohorts and substantially lower performance in many non-European populations.[63,64]

Future clinical implementation of schizophrenia genomic testing will require structured frameworks incorporating informed consent, genetic counseling, ancestry-specific calibration of risk models, clinical decision-support tools, and standardized communication of uncertainty. At present, polygenic risk scores should be viewed as risk-stratification tools rather than independent diagnostic instruments. Their responsible use will depend upon continued validation

across diverse populations and demonstration of meaningful clinical utility.

Pharmacogenomics and Personalized Treatment

Pharmacogenomic research has identified clinically relevant variation in genes affecting antipsychotic metabolism and therapeutic response. Variants in cytochrome P450 genes, particularly CYP2D6 and CYP2C19, influence drug metabolism rates, serum drug concentrations, and adverse-effect susceptibility. Genetic variation in DRD2, HTR2A, COMT, and glutamatergic signaling genes may also contribute to variability in treatment response and side-effect profiles.

Although pharmacogenomic testing is increasingly incorporated into precision medicine frameworks, implementation in psychiatry remains limited by inconsistent evidence, cost considerations, lack of standardized guidelines, and variable clinical utility across populations. Future translational approaches will likely require integration of genomic, transcriptomic, environmental, and longitudinal clinical data to support individualized treatment strategies.[60]

Implementation Pathway for Psychiatric Genomics

Responsible clinical implementation of schizophrenia genetic testing will likely require a staged framework consisting of: (i) pre-test genetic counseling and informed consent; (ii) standardized quality control and ancestry-specific calibration of polygenic risk models; (iii) integration of genomic information with clinical decision-support systems embedded within electronic health records; (iv) structured communication of probabilistic risk estimates and associated uncertainties; and (v) post-test counseling and longitudinal follow-up. Current evidence supports the use of PRS primarily for risk stratification and research applications rather than independent diagnostic decision-making. Future implementation should follow principles of clinical validity, clinical utility, transparency, and equity across diverse populations.

The growing clinical use of psychiatric genetic information raises important ethical and societal concerns. Potential issues include genetic discrimination, privacy breaches, stigmatization, inequitable access to testing, and psychological distress associated with probabilistic risk communication. Because schizophrenia risk arises through complex interactions between genetic and environmental factors, careful interpretation and counseling are necessary to avoid deterministic misconceptions. Robust regulatory frameworks, transparent informed-consent procedures, and equitable access policies will be essential for responsible translation of psychiatric genomics into clinical care.

Limitations and Future Directions

Despite substantial advances in psychiatric genomics, several limitations remain. Most schizophrenia genetic studies have been conducted in populations of predominantly European ancestry, limiting the generalizability of findings across global populations. Additionally, although numerous risk loci have been identified, the functional interpretation of many associated variants remains incomplete due to extensive linkage disequilibrium and the predominance of noncoding regulatory variation.

Current polygenic risk models possess limited predictive accuracy for clinical diagnosis at the individual level, and rare variant studies still require substantially larger sample sizes to identify additional high-confidence susceptibility genes. Furthermore, environmental exposures, epigenetic modifications, developmental trajectories, and gene–environment interactions remain incompletely understood.

Future research integrating whole-genome sequencing, single-cell multi-omics, longitudinal cohort studies, and functional experimental models will be essential for translating genetic discoveries into mechanistic insight and clinically actionable applications.[65,66]

An additional challenge involves the limited transferability of genomic prediction models across ancestries. Most schizophrenia GWAS and PRS development efforts have relied heavily on European-ancestry datasets, potentially reducing predictive accuracy and increasing health disparities when applied to underrepresented populations. Future studies should prioritize global recruitment strategies, cross-ancestry fine-mapping, ancestry-specific functional annotation, and equitable implementation frameworks to ensure that advances in psychiatric genomics benefit diverse populations.

Despite rapid advances in psychiatric genomics, polygenic risk scores are not currently suitable as stand-alone diagnostic tools. Their most realistic near-term application lies in probabilistic risk stratification, research participant enrichment, and integration with environmental, developmental, cognitive, and biomarker data. Clinical implementation should be accompanied by ancestry-aware modeling, independent validation, genetic counseling, and transparent communication of uncertainty.[62,67]

Public Health Implications

The significance of schizophrenia for public health is evident, and the justification for looking for genetic causes is powerful. Research on schizophrenia has never been simple; while the current era of studying the genetics of schizophrenia offers some intriguing hints, definitive answers are still pending.

Results from the body of literature seem to be more than coincidental yet sufficiently diverse to make "hard" replication difficult. The conflicting effects of Type 1 and Type 2 errors may be the cause of the current hazy perception of this material. It is not yet possible to fully incorporate this body of work into clinical practice.[62,68] But it is not premature and must let patients know that research is progressing and that, in the next five to 10 years, there may be new discoveries about etiology, pathophysiology, and treatment. On a broader scale, how a society treats mentally ill people reflects that civilization's humanity; in many countries, this is not flattering. This poor reflection might improve if genetic discoveries continue to improve

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understanding of biological pathways contributing to schizophrenia risk.[57,61,67]

Conclusion

Schizophrenia is a highly polygenic and biologically complex neuropsychiatric disorder shaped by the combined effects of common variants, rare coding mutations, copy number variants, and de novo genetic alterations. Advances in GWAS, exome sequencing, cross-ancestry studies, and functional genomics have substantially improved understanding of the molecular architecture underlying disease susceptibility. Importantly, diverse forms of genetic variation converge on shared neurodevelopmental and synaptic pathways involving glutamatergic neurotransmission, calcium signaling, chromatin remodeling, immune regulation, and synaptic plasticity.[56,58,59,62]

Recent integration of multi-omic datasets, single-cell transcriptomics, and functional annotation strategies has enabled increasingly precise characterization of the biological mechanisms linking genetic risk to neuronal dysfunction. At the translational level, polygenic risk scores and pharmacogenomics hold promise for personalized psychiatry, although substantial challenges remain regarding predictive performance, ancestry bias, implementation, and ethical considerations.

Future progress will depend on globally representative cohorts, integrative systems biology approaches, and longitudinal functional studies capable of bridging statistical genetic associations with mechanistic insight and clinically actionable interventions.

Figure and Data Provenance Statement

Figures 1–5 are conceptual illustrations created by the authors for educational and synthesis purposes. Unless explicitly stated otherwise, figures are not derived from original datasets and should not be interpreted as presenting novel experimental results. Quantitative values and biological concepts summarized in the figures are based on findings reported in the cited literature.

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