Gene Expression **2026** vol. 25(4) | e00006
DOI: 10.14218/GE.2026.00006

Editorial

Beyond Discovery: Leveraging the Genetic Architecture of Schizophrenia for Mechanistic Stratification and Precision Psychiatry

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Received: March 21, 2026 | **Revised:** July 23, 2026 | **Accepted:** September 09, 2026 | **Published online:** September 20, 2026

The past decade has witnessed substantial advances in psychiatric genetics, fundamentally altering our biomedical understanding of severe mental illness. Through large international collaborations, including the Psychiatric Genomics Consortium and the Schizophrenia Exome Sequencing Meta-analysis, the genetic architecture of schizophrenia has been characterized in increasing detail.[1,2] We now recognize schizophrenia as a highly polygenic and biologically heterogeneous disorder, influenced by the combined effects of common GWAS-associated variants, rare copy-number variants, and ultra-rare coding variants affecting genes such as *SETD1A* and *GRIN2A*.[1,2] In our view, these discoveries suggest that the field is increasingly moving beyond simply cataloging genetic risk toward translating genomic architecture into clinically meaningful biological stratification.

However, as we progress through the latter half of the 2020s, the biomedical community faces a substantial translational challenge. While our catalog of risk variants is vast (including specific high-risk genes such as *SETD1A* and *GRIN2A*), clinical outcomes remain suboptimal.[1,2] Up to one-third of diagnosed patients develop treatment-resistant schizophrenia, and standard pharmacological interventions, primarily relying on dopamine D2 receptor antagonists, have not undergone a fundamental conceptual evolution in decades. The prevailing diagnostic paradigm that treats schizophrenia as a single, monolithic clinical entity is increasingly inadequate to capture its underlying biological heterogeneity. We therefore propose a shift from mere discovery of susceptibility genes toward rigorous mechanistic stratification of patients based on their integrated multi-omic profiles (Fig. 1).

Historically, translational efforts have focused primarily on polygenic risk scores (PRS).[3] Although PRS aggregates the effects of thousands of common variants, its value lies less in individual disease prediction than in defining clinically meaningful disease trajectories.[2,3] In our view, PRS should therefore evolve from a probabilistic risk metric into a tool for biological stratification that complements rare-variant analysis and functional genomics.

Emerging evidence, including preliminary findings from recent longitudinal work and systematic reviews, illustrates this potential.[3,4] For example, preliminary findings from the SUPER-Finland Study suggest that higher schizophrenia PRS is associated with poorer global functioning, reduced functional recovery during hospitalization, and an increased likelihood of unfavorable clinical trajectories.[4] Interestingly, integrating non-psychiatric polygenic liabilities, such as educational attainment, was reported to improve prognostic resolution. In short, these preliminary findings warrant further investigation of PRS as a potential tool for patient stratification beyond disease-risk prediction.[3,4] The genetic architecture of schizophrenia has the potential to inform future personalized treatments. Functional studies of schizophrenia risk genes such as SETD1A may help link genetic findings to cellular phenotypes.[5]

To operationalize this complexity, multivariate PRS-based clustering approaches are being explored to define clinically relevant schizophrenia subgroups. Preliminary findings from approaches such as PRScope suggest that patients may be stratified into subgroups with distinct genetic architectures and clinical trajectories.[6] For example, a biotype characterized by high neuroticism and depression PRS together with low cognitive performance has been associated with greater disease severity, treatment refractoriness, and increased clozapine use.[3,6] We think that this type of molecular subclassification represents a promising avenue for further investigation in precision psychiatry.

Recognizing the limitations of case-control designs in predicting these specific outcomes, the field is shifting toward within-case molecular genetics. Initiatives like the GENios program, harmonizing data from over 30,000 genotyped participants, are actively targeting real-world outcomes such as antipsychotic treatment response, long-term occupational functioning, and hospital admission frequency.[7]

While polygenic background may contribute to broad clinical trajectories, rare-variant functional studies may provide additional mechanistic insight. Current findings implicate several neurobiolo-

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How to cite this article: Ardicli S, Senturk N, Babayev H. Beyond Discovery: Leveraging the Genetic Architecture of Schizophrenia for Mechanistic Stratification and Precision Psychiatry. *Gene Expr* 2026;25(4):e00006. DOI: https://doi.org/10.14218/GE.2026.00006.

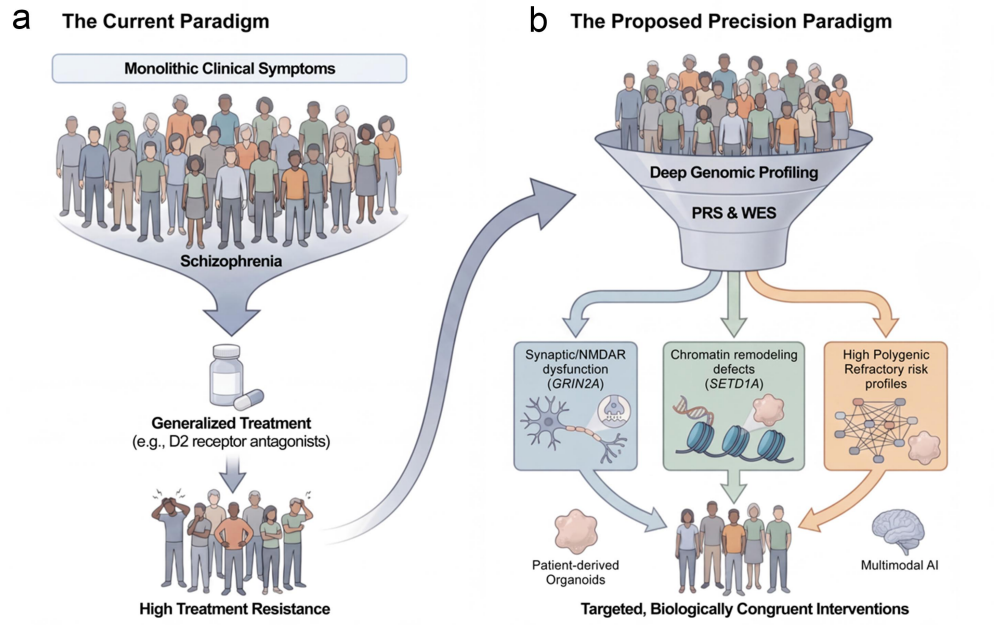

Fig. 1. Conceptual shift from diagnostic genetics to mechanistic stratification in schizophrenia. (a) The Current Paradigm: Large, heterogeneous patient populations are grouped by monolithic clinical symptoms and given generalized "one-size-fits-all" treatments (e.g., D2 receptor antagonists) regardless of underlying polygenic burden or rare-variant architecture, leading to high rates of treatment resistance. (b) The Proposed Precision Paradigm: Patients undergo deep genomic profiling combining polygenic risk scores (PRS) and whole-exome sequencing (WES). This proposed framework could support stratification into mechanistically informed subgroups (e.g., synaptic/NMDAR dysfunction via *GRIN2A*, chromatin remodeling defects via *SETD1A*, or high polygenic refractory-risk profiles), potentially linking patients to targeted, biologically informed interventions after appropriate validation, with patient-derived organoids and multimodal AI serving as investigational tools. The illustration was created in Illustrae (https://illustrae.co/) and edited manually. AI, artificial intelligence; D2, dopamine D2 receptor; NMDAR, N-methyl-D-aspartate receptor; PRS, polygenic risk score.

gical domains in schizophrenia pathophysiology:

Chromatin remodeling and epigenetic dysregulation: Rare loss-of-function variants in *SETD1A* have been associated with a substantial risk of schizophrenia.[8,9] Such variants can result in nonsense-mediated decay and *SETD1A* haploinsufficiency.[9] In CRISPR/Cas9-engineered human induced pluripotent stem cell (iPSC)-derived neuronal models, *SETD1A* haploinsufficiency has been shown to alter dendritic complexity and neuronal network activity.[5,9]

Glutamatergic synaptic signaling: Damaging variants in *GRIN2A*, which encodes the GluN2A subunit of the NMDA receptor, have been associated with increased risk of schizophrenia.[1] Experimental studies using *Grin2a*-deficient mouse models have demonstrated brain-region-specific alterations in neuronal activity, including reduced activity in the prefrontal cortex and increased activity in the hippocampus and striatum, together with altered glutamatergic and dopaminergic signaling.[10]

Inhibitory signaling and structural anomalies: Recent whole-exome sequencing evidence has implicated *SLC6A1* and *KLC1* in schizophrenia, with the associations for both genes driven predominantly by damaging missense variants.[11] *SLC6A1* encodes the GABA transporter GAT-1, and functional characterization of schizophrenia-associated *SLC6A1* missense variants has demonstrated loss-of-function effects, including reduced GABA uptake.[12] Although *KLC1* encodes a kinesin light-chain component involved in intracellular transport, the functional consequences of schizophrenia-associated *KLC1* missense variants remain to be established.[11] Furthermore, structural variation involving *C4A* at the MHC locus has been associated with increased complement activity and excessive synaptic pruning.[13]

This genetic architecture is consistent with viewing schizophrenia as a neurodevelopmental disorder with origins that may begin in utero. Spatiotemporal transcriptomic studies of the developing human cortex demonstrate dynamic, stage- and cell-type-specific gene-regulatory programs across prenatal cortical development and subsequent neuronal maturation. These findings provide a framework for investigating how disruptions in neurodevelopmental and synaptic programs may contribute to later disease vulnerability.[14]

Crucially, genetic liability may combine additively with environmental factors such as childhood adversity and cannabis use. In the EUGEI first-episode study, no significant interaction was detected between polygenic and polyenvironmental scores, while the overall findings were consistent with an additive liability-threshold model.[15]

Bridging the translational gap may benefit from advances in *in vitro* modeling, particularly patient-derived 3D cerebral and cortical organoids. Studies using patient-derived iPSCs have demonstrated that cerebral organoids can capture neurodevelopmental and cell-specific abnormalities associated with schizophrenia.[16] Recent methodological approaches have specifically focused on minimizing necrotic-core formation in iPSC-

derived cortical organoids.[17] These systems may ultimately provide complementary platforms for investigating patient-specific disease mechanisms, while their potential use for evaluating differential therapeutic responses will require further validation.

Integrating whole-exome sequencing, PRS, organoid transcriptomics, neuroimaging, and other high-dimensional datasets will increasingly benefit from multimodal artificial intelligence (AI) approaches designed to identify complex biological relationships that may be difficult to capture using conventional analytical approaches. We believe that AI should function not merely as a predictive tool but as an integrative framework linking genomic, molecular, and clinical data to enable biologically informed patient stratification. Reflecting this transition, the U.S. Food and Drug Administration and European Medicines Agency jointly issued the Guiding Principles of Good AI Practice in Drug Development in 2026, emphasizing human-centric design, risk-based approaches, data governance, and lifecycle management.[18]

Embracing this stratified framework may require complementing large, symptom-based clinical trials in which investigational interventions are tested broadly across highly heterogeneous, unstratified cohorts. Testing mechanism-directed interventions in biologically heterogeneous populations may dilute treatment effects and reduce statistical power. We anticipate that future precision psychiatry may increasingly incorporate smaller, genetically or biologically enriched trial designs, although such approaches remain investigational. Therapeutic efficacy may be more informative to evaluate within mechanistically homogeneous subgroups. As an example of biologically informed intervention development, the ongoing ATHENA trial at the University of Geneva is evaluating neuronavigated accelerated intermittent theta-burst stimulation targeting cerebellar circuitry in patients with schizophrenia spectrum disorders and negative symptoms (ClinicalTrials.gov identifier NCT06341517).[19] Importantly, this trial is not based on polygenic biotype selection but rather illustrates the broader movement toward mechanism-informed therapeutic targeting.

In conclusion, the genetic architecture of schizophrenia has become an increasingly informative framework for understanding neurodevelopmental, epigenetic, and synaptic mechanisms. Large-scale genomic discovery has provided a substantial foundation for translational research. A key next step is to determine how these findings can be translated into clinically meaningful stratification. By integrating polygenic trajectories, rare-variant pathobiology, and emerging technologies such as patient-derived organoids and multimodal AI, we have an opportunity to better characterize the clinical heterogeneity of schizophrenia.[1,2] Recognizing and acting upon distinct genetic biotypes represents one of the most promising paths toward realizing precision psychiatry.

Acknowledgments

None.

Funding

This work received no specific funding.

Conflict of interest

The authors declare no financial or non-financial competing interests related to the subject matter.

Author contributions

Study conception, literature review, and writing of the manuscript (SA, NS, HB). All authors have approved the final version and publication of the manuscript.

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