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# Update on the genetic architecture of schizophrenia

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**Abstract:** A long-established hypothesis is that schizophrenia has a strong genetic component. In the early 1990s, the first genetic variant that substantially increases risk for psychosis was identified. Since this initial reporting of deletions in the chromosomal region 22q11.2, nearly two decades passed until substantial insights into schizophrenia's genetic architecture were gained. Schizophrenia is a polygenic disorder and genetic risk is conferred by both common and rare alleles distributed across the genome. A small number of rare, deleterious copy number variants (CNVs) are associated with moderate to substantial increases in individual risk to schizophrenia. These deletions and duplications are also associated with a range of neurodevelopmental disorders. The diagnostic investigation of CNVs in patients with schizophrenia is likely to represent one of the first examples of genetic testing in clinical psychiatry. The prerequisites for this are currently being defined.

**Keywords:** intellectual disability, autism spectrum disorders, *SETD1A*, genome-wide genotyping array

**Zusammenfassung:** Seit langem ist bekannt, dass Schizophrenie gehäuft in Familien auftritt. Ein Beitrag genetischer Faktoren zur Krankheitsentstehung wird seither angenommen. Anfang der 1990 Jahre wurde der erste replizierbare Psychose-relevante Risikofaktor identifiziert. Seit der ersten Publikation von Deletionen in der chromosomalen Region 22q11.2 vergingen fast zwei Jahrzehnte bis weitere wesentliche Einblicke in die genetischen Grundlagen der Schizophrenie gelangen. Schizophrenie ist eine polygene Erkrankung. Die identifizierten genetischen Faktoren umfassen das gesamte allelische Spektrum und der Nachweis einer Krankheitsassoziation gelang für häufige und seltene Varianten. Für eine Handvoll seltener Deletionen und Duplikationen ist ein moderates bzw. hohes Erkrankungsrisiko beschrieben. Diese sind im Zusammenhang mit psychomotorischen Entwicklungsstörungen bereits bekannt. Die diagnostische Untersuchung seltener

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Deletionen/Duplikationen bei Patienten mit Schizophrenie wird wahrscheinlich eines der ersten Beispiele klinischer Anwendung sein, hierfür werden derzeit die notwendigen Voraussetzungen definiert.

**Schlagwörter:** Intelligenzminderung, Autismus-Spektrum-Störungen, *SETD1A*, genomweiter Genotypisierungs-Array

## Introduction

Schizophrenia is a severe neuropsychiatric disorder with a lifetime prevalence of ~1%. Patients with schizophrenia display a broad range of symptoms which include hallucinations, delusions, disorganized speech and/or behavior, and negative symptoms such as a blunted affect [1]. Schizophrenia is a clinical diagnosis and currently there is no single clinical or laboratory test available to confirm or rule out the diagnosis. Patients are offered a multiprofessional treatment that includes antipsychotic medication, psychoeducation, and psychotherapy [2]. Schizophrenia is a multifactorial disorder with both genetic and environmental factors contributing to its development. The genetic component is strong. Heritability estimates range between 60–80% [3, 4]. In the early 1990s, deletions in the chromosomal region 22q11.2 were identified to substantially increase the risk for psychosis [5]. Since the reporting of this first unequivocal genetic risk factor for schizophrenia, nearly two decades passed before substantial insights into disease-relevant biological mechanisms were gained [6–12]. The present article provides a concise overview of the current understanding of the genetic architecture of schizophrenia.

## Complex genetic architecture

In the 1990s and early 2000s, numerous schizophrenia candidate gene studies were conducted with limited success. Major technological advances (e.g., cost-effective array-based genome-wide genotyping and next-generation sequencing technologies), deciphering the sequence of the human genome, and the successful establishment of international science consortia (e.g., Psychi-

atric Genomics Consortium, PGC) [13–15] were the main drivers of our now improved understanding of the genetic underpinnings of schizophrenia.

The systematic, large-scale genetic analyses revealed that schizophrenia – in addition to being clinically heterogeneous – is a genetically heterogeneous disorder. It has a complex genetic architecture. Genetic risk is conferred by both common and rare alleles distributed across the genome (i. e., it is a polygenic disorder).

## Common variants associated with schizophrenia

In 2014, arguably the most groundbreaking discovery in schizophrenia genetics was published. The Schizophrenia Working Group of the PGC reported the results from the then largest genome-wide association study (GWAS). In this study, genome-wide genotype data from more than 37,000 patients with schizophrenia and 113,000 controls were analyzed. This led to the identification of 128 genome-wide significant variants (single nucleotide polymorphisms, SNPs) that were distributed across 108 independent genomic loci. Of these loci, 75% included protein coding genes [11, 16]. Even though each identified variant conveys only a small risk, the study provides important insight into the biological underpinnings of schizophrenia. Associations were enriched for brain-expressed genes and genes expressed in tissues relevant for immunity. The latter, together with the strongest association signal being located in the MHC region, supports the hypothesized link between schizophrenia and the immune system [11].

Furthermore, associations in several genes relevant for glutamatergic neurotransmission and the *DRD2* gene point to well-established and potentially new therapeutic drug targets. The *DRD2* gene encodes the dopamine D2 receptor, which is the therapeutic target of antipsychotic medication [11, 16]. Additional notable associations include genes relevant for glutamatergic neurotransmission, synaptic plasticity, and genes encoding voltage-gated calcium channel subunits [11].

In a subsequent GWAS (currently the largest genetic study of schizophrenia), data from more than 5,000 patients with schizophrenia and 18,000 controls were combined with independent data from the PGC. A total of 179 genome-wide significant SNPs located in 145 loci were identified. Of these, 50 associated loci were novel and 93 were genome-wide significant in the GWAS previously published by the PGC [16, 17]. The association signal was highly enriched among loss-of-function (LoF) intolerant

genes. Systems genomics analyses highlighted six gene sets that were independently associated with schizophrenia. These gene sets included (i) targets of the fragile X mental retardation protein (FMRP), (ii) abnormal behavior, (iii) abnormal nervous system electrophysiology, and (iv) voltage-gated calcium channel complexes [17].

Calculating polygenic risk scores (PRS) in order to stratify patients (e. g., in terms of course of disorder, prognosis, or treatment response) has gained traction [18]. PRS are a tool designed to capture the cumulative effects of numerous genetic loci into a single quantitative metric [19]. They are calculated using the weighted sum of the number of risk alleles carried by an individual. The risk alleles and their weights are derived from GWAS [18]. Currently, data on their potential use in clinical psychiatry are ambiguous [19–22]. Using PRS in a clinical setting is *not recommended* (<https://ispg.net/genetic-testing-statement/>). Large-scale, multi-ethnic studies are essential prior to considering the application of PRS in a non-research context [20, 22, 23]. However, PRS are an important research tool as they provide important insights into phenotypic correlations and inform research, e. g., on psychiatric endophenotypes [19].

## Copy number variants are relevant in a subset of patients

In the early 1990s, deletions in the chromosomal region 22q11.2 were reported to substantially increase the risk for psychosis [5]. The identification of additional risk-associated CNVs was hampered by limited sample sizes. In 2017, the worldwide largest schizophrenia CNV analysis to date (21,000 patients with schizophrenia and 20,000 controls) identified genome-wide significant evidence for deletions and duplications in eight loci: 1q21.1, 2p16.3, 3q29, 7q11.2, 15q13.3, distal 16p11.2, proximal 16p11.2, and 22q11.2. The CNVs have moderate to substantial effect sizes (odds ratio ~4–65). Approximately 1% of patients were reported to carry one of these deleterious deletions/duplications. Suggestive evidence was identified for eight additional susceptibility and protective loci [9]. The identified CNVs are pleiotropic; for carriers of the schizophrenia-associated deletions and duplications, the risk of developing any childhood-onset neurodevelopmental disorder is significantly higher than the risk of developing schizophrenia [24, 25]. Some of the schizophrenia-associated CNVs alter fecundity [26]. The decrease in the number of offspring in the CNV carriers correlates highly

with the penetrance of the deletions and duplications associated with neurodevelopmental disorders [26, 27]. One hypothesis is that unaffected (no diagnosis of a neurodevelopmental disorder) CNV carriers have deficits in socializing and forming families, likely due to behavioral, cognitive, and medical issues [27].

A study conducted in the UK Biobank showed that the schizophrenia-associated CNVs are associated with some degree of cognitive impairment, even among individuals without a neurodevelopmental disorder (including schizophrenia). The reduction in cognitive performance may be subtle. However, CNV carriers had significant disadvantages in educational attainment and hence the ability to earn income in adult life compared with non-CNV carriers [27]. Furthermore, CNVs have a profound impact on medical health and mortality. This includes hypertension, obesity, diabetes mellitus, and renal failure. Clinicians need to plan their patients' medical management accordingly, even in apparently unaffected CNV carriers [28]. As expected, the diagnostic yield for deleterious CNVs substantially increases in patients with a "syndromic form of psychiatric illness," i. e., in patients with a dual diagnosis of schizophrenia and intellectual disability (ID)/autism spectrum disorder (ASD) [29–33]. Recently, the first study attempting to identify phenotypic information that might flag patients with schizophrenia as carriers of pathogenic CNVs was published. The authors had access to phenotype data that were collected using standard clinical assessments. Clinical features that successfully modeled positive CNV carrier status were (i) having a history of a specific learning disability such as dyslexia, dyscalculia, or dysgraphia; (ii) a history of developmental delay; and (iii) a comorbid neurodevelopmental diagnosis such as ASD, ID, or epilepsy [24].

With the exception of CNVs in 2p16.3 (*NRXN1*), the schizophrenia-associated deletions and duplications span multiple genes. Next-generation sequencing facilitates the analysis of smaller CNVs and their relevance to psychiatric disorder [34].

## Exome sequencing provides further insights

Next-generation sequencing, currently predominantly exome sequencing, provides further insights into the biological mechanisms underlying schizophrenia. Patients with schizophrenia have an increased burden of ultra-rare, putatively protein damaging variants compared with controls [7]. Furthermore, patients have an increased burden of de

novo LoF variants [7, 12, 16]. The rare coding variants are enriched in specific gene pathways, e. g., in synaptic function [6, 7, 10, 16]. The pathogenic variants detected among patients with schizophrenia overlap with pathogenic variants reported for ASD and ID [6].

The first (and currently only) gene to be implicated in schizophrenia at Bonferroni-corrected genome-wide levels of statistical significance is *SETD1A*. Rare LoF variants were strongly associated with schizophrenia in a study comprising more than 7,000 patients and 13,000 controls. Interestingly, seven of the ten patients with schizophrenia carrying an LoF variant were reported to have learning difficulties. The gene *SETD1A* encodes one of the methyltransferases that catalyze the methylation of lysine residues in histone H3. This supports the hypothesis that chromatin remodeling is an important molecular mechanism in the pathogenesis of schizophrenia [12].

Furthermore, exome sequencing facilitates the identification of inborn errors of metabolism (IEM). There is an increasing awareness that IEM might manifest beyond early childhood with psychiatric symptoms as the first indicator of the disorder. Targeted sequencing of genes relevant for IEM or exome sequencing might be warranted in patients with early onset psychosis [35, 36].

## Future challenges and perspectives

Despite major breakthroughs, the identified variants account only for part of schizophrenia's heritability, with approximately 20–30% of variance explained [9, 11, 17]. Historically large sample sizes are essential to further unravel the genetic underpinnings of schizophrenia [15, 37]. The recruitment of individuals is an ongoing international effort. It includes sampling a diverse range of ancestries (identification of new genetic associations due to different genetic architectures between populations) and using new ascertainment strategies (e. g., linking electronic health records to genomic data) [15, 37–39].

Gene–environment interactions might partially explain schizophrenia's missing heritability. Genetic liability to schizophrenia might cause individuals to be more sensitive to environmental exposures or to have higher exposure rates [40]. Assessing the role of environmental factors in moderating genetic vulnerability is gaining traction and large cohorts with rich information on environmental exposures are being collected [41, 42]. The European Network of National Schizophrenia Networks Studying Gene–Environment Interactions (EUGENIE) study provided

evidence for an additive interaction between schizophrenia PRS and, e. g., exposure to early-life adversities and the presence of lifetime regular cannabis use [41]. Supplementing the available genetic data with genome-wide methylation data will provide further insights into the biological mechanisms underlying schizophrenia.

For the vast majority of identified variants, it is not known how they confer risk to schizophrenia. A broad range of methods is used to elucidate the molecular and cellular mechanisms relevant for the pathogenesis of schizophrenia [38]. These include genome editing in model organisms and human-induced pluripotent stem cell technology [43, 44].

Large-scale genetic studies demonstrated shared genetic risk across psychiatric disorders. Common variant analyses provided strong evidence particularly for genetic overlap between schizophrenia and bipolar disorder [8, 45, 46]. The identified risk variants aggregate in specific pathways such as histone methylation processes, postsynaptic density, and multiple neuronal and immune signaling pathways. The implicated pathways are shared between disorders [47]. Rare variant studies showed shared genetic risk between schizophrenia and neurodevelopmental disorders such as ASD and ID [6, 7, 12, 30, 31, 48]. Future research projects need to integrate communities researching childhood-onset neurodevelopmental disorders and adult-onset psychiatric disorders [16].

The diagnostic investigation of CNVs in patients with schizophrenia is likely to represent one of the first examples of genetic testing in clinical psychiatry. The prerequisites for this are currently being defined on both a European (EnGagE Network, Enhancing Psychiatric Genetic Counselling, Testing, and Training in Europe; CA17130, [www.cost.eu/actions/CA17130](http://www.cost.eu/actions/CA17130)) and an international level (Genetic Testing Committee of the International Society of Psychiatric Genetics; [www.ispg.net/](http://www.ispg.net/)).

While anticipating the publication of the first recommendation for genetic testing in patients with schizophrenia (e. g., in patients with a history of developmental delay, early-onset psychosis, or treatment-resistant psychosis), the consensus statement on the genetic work-up of patients with ID and/or ASD await implementation into routine psychiatric care [49]. While in most European countries chromosomal microarrays and/or exome sequencing are standard of care for children with these diagnoses, diagnostic genetic testing is rarely offered to adult patients with neurodevelopmental disorders.

Identifying a deleterious CNV in an adult patient with a syndromic form of psychosis might inform clinical management [50, 51, 62]. For example, patients with a 22q11.2 deletion are at increased risk for serious adverse events

to clozapine treatment and have a lowered seizure threshold. Medication (e. g., anticonvulsants) might exacerbate hypocalcemia [51–53]. Offering genetic testing to adult patients with impaired cognition will challenge the genetic counseling process [54]. More studies are warranted on factors influencing the phenotype expression and penetrance of the identified deleterious CNVs [27, 55–59]. Furthermore, case reports and case series containing both a comprehensive initial assessment of the patient with a psychiatric disorder and a systematic description of the longitudinal course and the impact of therapeutic efforts are warranted [60]. Interdisciplinary clinical management in centers for rare disorders with psychiatric manifestations is anticipated.

An improved understanding of the genetic architecture of schizophrenia and its underlying biological mechanisms will further facilitate patient stratification. Genotype-targeted treatment might improve patient care [61].

## Conclusions and implications for clinical practice

- Schizophrenia is a genetically heterogeneous disorder. Large-scale studies have provided substantial insight into the disorder's complex genetic architecture.
- For the majority of patients with schizophrenia, common variants are the main genetic contributor to the disorder. Currently, polygenic risk scores have no clinical utility.
- A subset of patients carry rare deleterious copy number variants (CNVs) with larger effect sizes. These CNVs are also associated with neurodevelopmental disorders such as intellectual disability (ID) and autism spectrum disorder (ASD).
- Genome-wide CNV testing should be offered to patients with schizophrenia and ID/ASD/organ malformations. Efforts to establish genetic testing in clinical psychiatry are under way.
- Patients and their family members tend to overestimate the recurrence risks for psychiatric disorders. Genetic counseling might be particularly useful in multiplex families with psychiatric (and) neurodevelopmental disorders.

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