

Overlap between genetic variants associated with schizophrenia spectrum disorders and intelligence quotient: a systematic review

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Background: To study whether there is genetic overlap underlying the risk for schizophrenia spectrum disorders (SSDs) and low intelligence quotient (IQ), we reviewed and summarized the evidence on genetic variants associated with both traits. **Methods:** We performed this review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and preregistered it in PROSPERO. We searched the Medline databases via PubMed, PsycInfo, Web of Science and Scopus. We included studies in adults with a diagnosis of SSD that explored genetic variants (single nucleotide polymorphisms [SNPs], copy number variants [CNVs], genomic insertions or genomic deletions), estimated IQ and studied the relationship between genetic variability and both traits (SSD and IQ). We synthesized the results and assessed risk of bias using the Quality of Genetic Association Studies (Q-Genie) tool. **Results:** Fifty-five studies met the inclusion criteria (45 case–control, 9 cross-sectional, 1 cohort), of which 55% reported significant associations for genetic variants involved in IQ and SSD. The SNPs more frequently explored through candidate gene studies were in *COMT*, *DTNBP1*, *BDNF* and *TCF4*. Through genome-wide association studies, 2 SNPs in *CHD7* and *GATAD2A* were associated with IQ in patients with SSD. The studies on CNVs suggested significant associations between structural variants and low IQ in patients with SSD. **Limitations:** Overall, primary studies used heterogeneous IQ measurement tools and had small samples. Grey literature was not screened. **Conclusion:** Genetic overlap between SSD and IQ supports the neurodevelopmental hypothesis of schizophrenia. Most of the risk polymorphisms identified were in genes relevant to brain development, neural proliferation and differentiation, and synaptic plasticity.

Introduction

Schizophrenia spectrum disorders (SSDs) are characterized by hallucinations, delusions, disorganized thinking, negative symptoms and cognitive dysfunctions that compromise functionality.^{1,2} They differ from each other according to type of symptoms, duration and etiology; schizophrenia is the most severe and disabling disorder, with a lifetime prevalence of 0.7% to 0.9%.³ The etiology of SSD is unknown, but its onset is influenced by an interaction of genetic and environmental factors.⁴ Genetic studies have estimated the heritability of schizophrenia to be approximately 80%,^{5,6} which is explained in part by the global effect of thousands of single nucleotide polymorphisms (SNPs; SNP heritability = 24%).⁷ In addition, the polygenic burden of risk variants — so-called polygenic risk scores — explains 7.3% of the variance in risk for schizophrenia according to the most recent estimates.^{7–9}

In recent years, there has been widespread interest in establishing endophenotypes of SSD that allow for its identification

through observable and quantitative traits.^{10,11} One of these candidate endophenotypes is IQ,^{12–16} a quantitative score obtained from a standardized intelligence test that represents an individual's intellectual ability.¹⁷ Thanks to this quantitative estimate of general cognitive function, it is possible to make comparisons between individuals, so it is common to use IQ scores to assess intelligence in the population.¹⁷ Current evidence indicates that IQ is heritable, and that its genetic architecture is highly polygenic.^{18–21} In addition, people with SSD have shown poorer intellectual performance than healthy controls,^{22,23} findings that in some cases are already present in childhood.²⁴ Along the same line, it has been demonstrated that adolescents at high risk of psychosis exhibit a lower IQ than healthy controls,²⁵ and that the unaffected relatives of patients with SSD present similar deficits.²⁶ Taken together, this evidence indicates that SSDs might be caused by pathological neurodevelopment processes that would be observable as premorbid intellectual deficits.

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Genetic overlap between vulnerability to SSD and low intelligence has been identified in large studies involving people with schizophrenia¹⁰ and healthy participants.²⁷ This evidence is consistent with the findings of a population-based study in more than 100 000 participants that described significant associations between polygenic risk for schizophrenia and other neuropsychiatric disorders and poorer cognitive functioning, especially in processing speed and memory.²⁸ Accordingly, the large-scale genome-wide association study (GWAS) by Savage and colleagues²⁹ identified 205 genomic loci associated with intelligence, which they found to be enriched in genes expressed in the brain. Moreover, Ohi and colleagues³⁰ found that genetic factors differentiating schizophrenia from bipolar disorder were related specifically to low premorbid intelligence. Thus, the identification of genetic variants that contribute to risk of schizophrenia and low IQ could provide insights into the biological correlates of the disorder.

Generally, different GWASs have found that the genetic variants associated with both traits are enriched in genes expressed in the central nervous system, and that they participate in neurogenesis, regulation of nervous system development, neuronal differentiation and regulation of cell development.^{7,29,31} For instance, an SNP in the *DTNBP1* gene (rs1011313) has been related to both neurocognition and schizophrenia risk, probably because of its involvement in the glutamatergic system.³² Another locus associated with increased risk for schizophrenia and lower general cognition is *TCF20* (rs134873, intron variant), which encodes a transcriptional coregulator.³³ The authors of that study found that the risk allele of rs134873 was related to increased expression of *NAGA* (involved in the regulation of glycosylation-associated enzymes, glutamatergic and GABAergic systems³⁴) and decreased expression of *CYP2D6* (involved in serotonin and dopamine metabolism) in the human brain.³³

Other sources of genetic variation, such as copy number variants (CNVs), may also be involved in the etiology of schizophrenia and intellectual deficits, because patients with schizophrenia who had at least 1 rare CNV yielded low IQs.³⁵

Although several researchers have investigated the genetic variants associated with SSD and IQ, no systematic review has summarized the current findings. We believed that a compilation of results from original studies could contribute in different ways to the field of knowledge. A synthesis with no date limitation allowed us to understand the evolution of an area of research, contributing to a better level of scientific quality and reducing the possibility of bias. Furthermore, by comparing independent samples, a description of positive and negative results helped us to establish whether findings were consistent and could be generalized. Likewise, we wanted to include both candidate gene studies and GWASs to evaluate the replicability of results when using different methods. GWASs yield valuable results, because they have the advantage of reducing possible biases based on their lack of a pre-established hypothesis. However, both GWASs and candidate gene studies are subject to publication bias, because they are at risk of not being reported when the results are negative.

To answer the question of whether overlapping genetic variants underlie the risk of both SSD and low IQ, we aimed to analyze and summarize the findings of primary studies on genetic variants associated with both traits. These data will contribute to establishing IQ as a potential endophenotype for SSD, and to identifying future lines of research.

Methods

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PRISMA checklist in Appendix 1, available at www.jpn.ca/lookup/doi/10.1503/jpn.220026/tab-related-content).³⁶ It was registered in the International Prospective Registry of Systematic Reviews (PROSPERO; CRD42020218842), and a protocol was elaborated to guide the review process (<https://doi.org/10.21203/rs.3.rs-150210/v1>).

Eligibility criteria

We included the following types of studies: published genetic association studies based on IQ (GWASs or candidate gene studies) with an observational design, including cross-sectional, case-control and cohort studies. We considered only manuscripts published in English, but we imposed no restrictions on date of publication. We selected studies in adults with a diagnosis of SSD based on DSM² or ICD³⁷ criteria at any stage of disease (first episode of psychosis or chronic). We included studies that addressed the association between genetic variability and both traits (SSD and IQ) by exploring the following genetic variants: SNPs, CNVs, genomic insertions and genomic deletions. We included only studies that estimated participants' IQ using a standardized test. By including studies in patients with SSD that estimated IQ, we sought to guide the search strategy and selection process toward research that targeted the genetic overlap between both traits.

The following were reasons for exclusion from this review: animal model or cell line studies; studies not measuring the outcomes of interest (lacking genotyping, IQ estimation or their association); reviews or meta-analyses; not peer-reviewed; single-case studies; books, editorials or theses.

Search strategies and information sources

We established the design of the search strategy with the advice of an expert librarian from the University of Cantabria. We carried out the search in November 2020 and updated it in October 2021 in the electronic databases of Medline via PubMed, PsycInfo, Web of Science and Scopus.

In accordance with the PRISMA guidelines, we adapted the search strategy to the controlled format of each database when appropriate. For Medline, we used the MeSH format ("Schizophrenia" OR "Psychotic Disorders" OR "Psychosis") AND ("Genetic Variation" OR "Genetic Variant" OR "Polymorphism, Genetic" OR "Polymorphism, Single Nucleotide" OR "Polymorphism") AND ("Intelligence" OR "Intelligence

Quotient" OR "IQ"). For PsycInfo, we used the Thesaurus format (DE"Schizophrenia" OR "Psychotic Disorders" OR DE"Psychosis") AND ("Genetic Variation" OR "Genetic Variant" OR "Polymorphism, Genetic" OR "Polymorphism, Single Nucleotide" OR DE"Polymorphism") AND (DE"Intelligence quotient" OR "IQ"). We screened the Web of Science and Scopus databases using the above terms in free text, and we limited the results in Scopus by document type (article) and language (English) because of the large number of records obtained. We also examined the reference lists of the included articles to identify additional eligible studies.

Study selection and data collection process

After we had retrieved the database results, we recorded them in EndNote (Clarivate Analytics). After duplicate records had been eliminated, 2 reviewers (N.M.G., S.B.M.) screened each record independently by reviewing titles and abstracts. Then, the reviewers separately analyzed the full texts of eligible studies and selected those that met the inclusion criteria, selecting the final studies by consensus. Doubts or discrepancies were resolved between the reviewers, and if necessary, they consulted the postdoctoral researcher (E.S.S.) and the senior researcher (R.A.A.).

Data from the selected studies were recorded in a standardized table designed by the reviewers. The information extracted from each study included the author, the year of publication, the country of origin, the study design, genetic variants and genes investigated, the sample size (patients and healthy controls, if applicable), instruments for measurement of IQ, mean IQ and main findings. Each reviewer collected information from half of the included studies, and then the 2 reviewers exchanged records for verification by their partner.

Outcomes

Among genetic variants for SSD, we considered SNPs, CNVs, genomic insertions and genomic deletions. Only studies that reported the location of the genetic variant were included. For IQ outcomes, we considered a global intelligence score estimated using any standardized measure, such as the Wechsler Adult Intelligence Scale, the Wechsler Test of Adult Reading, the North American Adult Reading Test–Revised (NAART) or the Wechsler Abbreviated Scale of Intelligence.

All types of IQ were included: verbal, performance or full. Verbal IQ is an intelligence index estimated from results on tests of verbal comprehension and working memory; performance IQ is estimated from scores on tests of perceptual organization and processing speed; and full IQ provides a mean of both verbal and performance IQ.¹⁷

Quality assessment of primary studies

We used the Quality of Genetic Association Studies (Q-Genie) tool to assess risk of bias in the included studies.³⁸ Q-Genie is a questionnaire of 11 items rated on a 7-point Likert scale; a score of 1 indicates poor quality, and a score of 7 indicates excellent quality. The 11 items evaluate different categories,

including the rationale for the study, ascertainment of comparison groups, and technical and nontechnical classification of the genetic variants tested. Q-Genie allowed us to obtain a global score that indicated the overall quality of the study, which could be poor (scores ≤ 35 for studies with control groups and ≤ 32 for studies without control groups), moderate (scores between 35 and 45 for studies with control groups and between 32 and 40 for studies without control groups) or good (scores > 45 for studies with control groups and > 40 for studies without control groups).

Data synthesis

A narrative synthesis of the analyzed studies is presented in the results. For greater clarity and organization of the results, we grouped the findings into 2 sections, 1 on candidate gene studies and 1 on GWASs.

Results

We identified a total of 2438 records from database searching. After duplicates had been eliminated, 2153 results were screened for eligibility, of which 2007 were discarded because they met 1 of the exclusion criteria (3 book chapters, 9 letters to the editor, 24 case studies, 44 meta-analyses, 166 reviews, 226 animal or cellular models, and 1535 did not address the topic of interest). Of the 146 full-text articles we reviewed, 93 were excluded because they did not meet the inclusion criteria. We included 2 additional records from citation searching. In the end, we included 55 articles that explored genetic variants associated with both SSD and IQ in the present review (Figure 1).

Among the included studies, 47 (85.45%) had overall scores of good quality based on the Q-Genie tool, and 8 (14.55%) had scores of overall moderate quality. No study was of low quality (Appendix 1).

Of the 45 studies with a case–control design, 39 (86.67%) reported that patients with SSD had significantly lower IQs than healthy controls, regardless of the evaluation tool used. One of the remaining case–control studies found no significant differences, and the rest ($n = 5$) did not report participants' IQ. The included studies explored different polymorphisms, yielding heterogeneous results. However, the genes addressed most frequently using the candidate gene strategy were *COMT*, *BDNF*, *DTNBP1* and *TCF4*.

Fewer studies used a GWAS strategy; their findings are presented below.

Candidate gene studies

COMT

Seven studies examined the association of the *COMT* genotype with both SSD and IQ; 6 had a case–control design and 1 had a cross-sectional design. We found mixed results, as shown in Table 1. Four of the studies (57.14%)^{39–42} found no significant association between the SNP rs4680 (also known as the Val158Met polymorphism) and IQ in people with SSD. The other 3 studies (42.86%)^{43–45} did find significant associations. Green

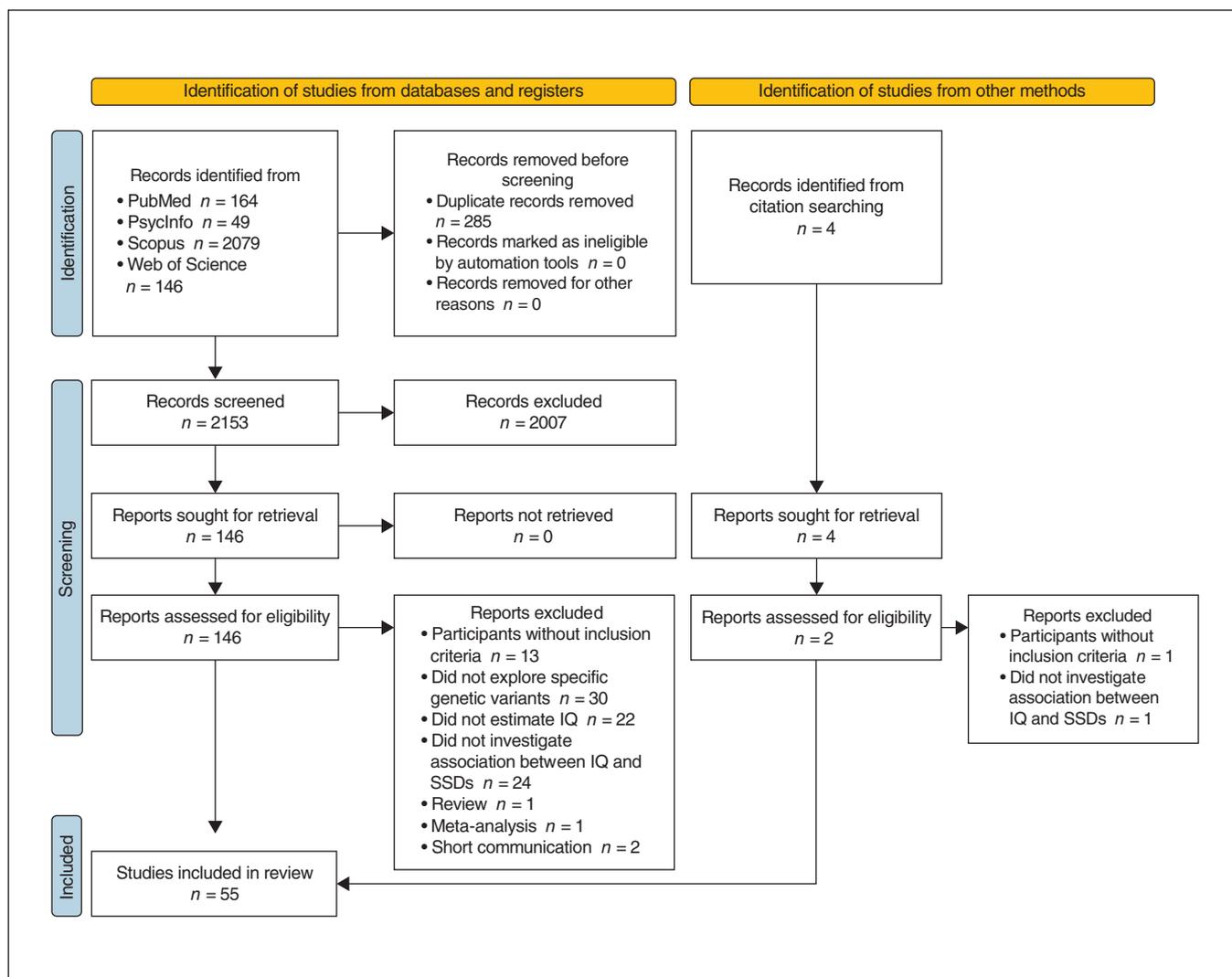


Figure 1: PRISMA 2020 flow diagram³⁶ for new systematic reviews which included searches of databases, registers and other sources. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SSD = schizophrenia spectrum disorder.

and colleagues⁴⁴ found that the Val158Met polymorphism was a significant predictor of IQ, because Val homozygotes had lower scores on the intelligence test. Two more studies reported similar results, but with certain specifications. Kontis and colleagues⁴⁵ found that *COMT* Val homozygotes had lower IQs, but this effect was reduced by interaction with the rs1801133 allele *MTHFR*-T. Rebollo-Mesa and colleagues⁴³ observed that the Val158Met polymorphism was significantly related to IQ only in patients who were taking antipsychotics: Val carriers taking a high dose of antipsychotic medication had lower IQs than Met carriers.

BDNF

Five studies explored the link between variations in the *BDNF* gene and IQ in patients with SSD (Table 2). All studies included a control group and focused on the Val-66Met polymorphism (rs6265). Three studies (60%)^{46,49,50}

reported negative results, but Chung and colleagues⁴⁷ and Lu and colleagues⁴⁸ found a significant correlation between the Val66Met SNP and patients' IQ. The Met allele was associated with lower IQ in patients with SSD in both studies, although in the case of Chung and colleagues,⁴⁷ this relationship lost significance after Bonferroni correction.

DTNBP1

Five studies targeted polymorphisms at *DTNBP1* (Table 3), of which 3 had a case-control methodology and 2 had a cross-sectional design. Two studies (40%) found no association between different SNPs in *DTNBP1* and patients' IQ;^{52,54} the remaining studies (60%) confirmed such an association.^{51,53,55} Burdick and colleagues⁵¹ observed that the genotype of 6 SNPs in *DTNBP1* (rs909706, rs1018381, rs2619522, rs760761, rs2619528 and rs1011313) was associated with intellectual decline in patients: carriers of the

Table 1: Studies exploring the *COMT* gene and IQ in patients with schizophrenia

| Polymorphism | Study | Design | Country | Ancestry* | Participants, <i>n</i> | | IQ measure | Mean IQ ± SD | | Association between polymorphism and IQ in patients with SSD |
|--------------------|--|-----------------|----------------|---------------|------------------------|------------------|-------------|---------------|------------------|--|
| | | | | | Patients | Healthy controls | | Patients | Healthy controls | |
| rs4680† | Galderisi et al. ³⁹ (2005) | Cross-sectional | Italy | Caucasian | 106 (schizophrenia) | NA | WAIS | NA | NA | No |
| rs4680 | Ho et al. ⁴⁰ (2005) | Case-control | United States | Caucasian | 159 (schizophrenia) | 84 | WAIS§ | 91.0 ± 12.45 | 109.0 ± 12.05 | No |
| rs4680 | Prata et al. ⁴¹ (2009) | Case-control | United Kingdom | 90% Caucasian | 42 (schizophrenia) | 48 | WAIS, WASI§ | 97.2 ± 16.4 | 118.2 ± 11.5 | No |
| rs4680 | Wirgenes et al. ⁴² (2010) | Case-control | Norway | Caucasian | 171 (SSD) | 340 | WASI§ | 103.5 ± 13.8 | 113.6 ± 9.9 | No |
| rs4680 | Rebollo-Mesa et al. ⁴³ (2011) | Case-control | United Kingdom | 84% Caucasian | 68 (SSD) | 208 | WAIS | NA | NA | Yes (only with antipsychotics) |
| rs4680 | Green et al. ⁴⁴ (2014) | Case-control | Australia | Caucasian | 617 (SSD) | 659 | WTAR§ | 97.49 ± 15.04 | 105.47 ± 10.67 | Yes |
| rs4680, rs1801133‡ | Kontis et al. ⁴⁵ (2013) | Case-control | Greece | NA | 90 (schizophrenia) | 55 | WAIS | 81.06 ± 11.35 | NA | Yes |

NA = not available; SD = standard deviation; SSD = schizophrenia spectrum disorder; WAIS = Wechsler Adult Intelligence Scale; WASI = Wechsler Abbreviated Scale of Intelligence; WTAR = Wechsler Test of Adult Reading.

*Terminology taken from the original articles.

†rs4680 is commonly known as the Val158Met polymorphism.

‡rs1801133 is located in the *MTHFR* gene.

§Patients had significantly lower IQs than healthy controls.

Table 2: Studies exploring the *BDNF* gene and IQ in patients with schizophrenia

| Polymorphism | Study | Design | Country | Ancestry* | Participants, <i>n</i> | | IQ measure | Mean IQ ± SD | | Association between polymorphism and IQ in patients with SSD |
|--------------|--------------------------------------|--------------|---------------|---|---------------------------------|------------------|------------|---------------|------------------|--|
| | | | | | Patients | Healthy controls | | Patients | Healthy controls | |
| rs6265† | Ho et al. ⁴⁶ (2006) | Case-control | United States | NA | 293 (SSD) | 144 | WAIS‡ | 91.49 ± 13.49 | 110.41 ± 11.66 | No |
| rs6265 | Chung et al. ⁴⁷ (2010) | Case-control | South Korea | East Asian | 101 (schizophrenia) | 50 | WAIS‡ | 102.45 ± 14.1 | 107.9 ± 10.4 | Yes (only before statistical correction) |
| rs6265 | Lu et al. ⁴⁸ (2012) | Case-control | China | East Asian | 112 (SSD) | 63 | WAIS‡ | 87.8 ± 14.7 | 113.4 ± 14.2 | Yes |
| rs6265 | Smith et al. ⁴⁹ (2012) | Case-control | Canada | 72% Caucasian, 10% South Asian, 9% East Asian, 9% Other | 58 (first episode of psychosis) | 39 | NAART | 100.4 ± 8.7 | NA | No |
| rs6265 | Abbasian et al. ⁵⁰ (2021) | Case-control | Iran | Asian | 71 (schizophrenia) | 88 | WAIS‡ | 85.48 ± 13.6 | 98.30 ± 15.12 | No |

NA = not available; NAART = North American Adult Reading Test; SD = standard deviation; SSD = schizophrenia spectrum disorder; WAIS = Wechsler Adult Intelligence Scale.

*Terminology taken from the original articles.

†rs6265 is commonly known as the Val66Met polymorphism.

‡Patients had significantly lower IQs than healthy controls.

CTCTAC haplotype demonstrated a significantly greater decline in IQ than noncarriers. Zinkstok and colleagues⁵³ found that carriers of the low-frequency allele in SNPs rs760761 (T) and rs2619522 (G) had lower IQs, and the common allele in

rs2619538 (A) was related to higher IQ. Varela-Gomez and colleagues⁵⁵ found that patients who were homozygotes for the risk genotype in rs2619539 (GG) and in rs3213207 (AA) had lower IQs.

Table 3: Studies exploring the *DTNBP1* gene and IQ in patients with schizophrenia

| Polymorphism | Study | Design | Country | Ancestry* | Participants, <i>n</i> | | | Mean IQ ± SD | | Association between polymorphism and IQ in patients with SSD |
|--|--|-----------------|---------------|--|------------------------|------------------|------------|---------------|------------------|--|
| | | | | | Patients | Healthy controls | IQ measure | Patients | Healthy controls | |
| rs909706, rs1018381, rs2619522, rs760761, rs2619528, rs1011313 | Burdick et al. ⁵¹ (2007) | Cross-sectional | United States | Caucasian | 183 (SSD) | NA | WRAT | NA | NA | Yes |
| rs2619539, rs3213207, rs261953 | Donohoe et al. ⁵² (2007) | Cross-sectional | Ireland | Caucasian | 52 (SSD) | NA | WTAR | 93.05 ± 11.85 | NA | No |
| rs2619539, rs3213207, rs1011313, rs2619528, rs760761, rs2619522, rs2619538 | Zinkstok et al. ⁵³ (2007) | Case-control | Netherlands | Caucasian, Turkish, Moroccan, Surinamese | 76 (FEP) | 31 | WAIS† | 86.7 ± 13.8 | 107.0 ± 15.5 | Yes (only rs2619528, rs760761, rs2619522, rs2619538) |
| rs261953 | Hashimoto et al. ⁵⁴ (2009) | Case-control | Japan | East Asian | 70 (schizophrenia) | 165 | WAIS† | 87.06 ± 18.86 | 109.73 ± 10.73 | No |
| rs2619539, rs2619528, rs2619538, rs3213207, rs760761 | Varela-Gomez et al. ⁵⁵ (2015) | Case-control | Spain | NA | 238 (FEP) | 47 | WAIS | NA | NA | Yes (only rs2619539 and rs3213207) |

FEP = first episode of psychosis; NA = not available; SD = standard deviation; SSD = schizophrenia spectrum disorder; WAIS = Wechsler Adult Intelligence Scale; WRAT = Wide Range Achievement Test; WTAR = Wechsler Test of Adult Reading.
 *Terminology taken from the original articles.
 †Patients had significantly lower IQs than healthy controls.

Table 4: Studies exploring the *TCF4* gene and IQ in patients with schizophrenia

| Polymorphism | Study | Design | Country | Ancestry* | Participants, <i>n</i> | | | Mean IQ ± SD | | Association between polymorphism and IQ in patients with SSD |
|--------------|--------------------------------------|-----------------|---------|-------------------------|------------------------|------------------|-------------|---------------|------------------|--|
| | | | | | Patients | Healthy controls | IQ measure | Patients | Healthy controls | |
| rs9960767 | Lennertz et al. ⁵⁶ (2011) | Cross-sectional | Germany | NA | 401 (schizophrenia) | NA | MWT-B, WAIS | 105.28 ± 17.7 | NA | No |
| rs2958182 | Zhu et al. ⁵⁷ (2013) | Case-control | China | East Asian | 526 (schizophrenia) | 421 | WAIS† | 96.01 ± 14.99 | 110.13 ± 11.6 | Yes |
| rs9960767 | Albanna et al. ⁵⁸ (2014) | Cross-sectional | Canada | 103 Caucasian, 70 Other | 173 (FEP) | NA | WAIS | 90.9 ± 15.25 | NA | No |

FEP = first episode of psychosis; MWT-B = Mehrfachwahl-Wortschatz Test B; NA = not available; SD = standard deviation; SSD = schizophrenia spectrum disorder; WAIS = Wechsler Adult Intelligence Scale.
 *Terminology taken from the original articles.
 †Patients had significantly lower IQs than healthy controls.

TCF4

Three studies assessed the relationship between IQ in patients with SSD and polymorphisms in *TCF4* (Table 4). Two of them (66.66%) were cross-sectional and did not find a significant association.^{56,58} In contrast, a study⁵⁷ with a case-control design observed that T-carrier patients at rs2958182 had higher IQs than A-carrier patients.

Other candidate genes

Twenty-nine studies explored candidate genes other than those mentioned above; 26 had a case-control design, 2 were cross-sectional and 1 was longitudinal. Of these, 16 studies (55.17%) reported significant associations be-

tween the investigated polymorphisms and patients' IQs in different directions (Table 5). In most cases, the minor frequent allele was associated with lower IQ in patients, including SNPs at *ANK3*,⁶¹ *CSMD1*,⁶⁵ *FOLH1*,⁶⁷ *GRM7*,⁶⁸ *GRM5*,⁶⁹ *MHC*,⁷³ *MIR137*,⁷⁴ *NOS1*,⁷⁵ *NRG1*,⁷⁷ *NRGN*⁷⁸ and *OXTR*.⁸² For *NRGN*,⁷⁸ an association with IQ was found only for the diplotype rs12807809-rs12278912, where the risk allele combination TG/TG was related to lower IQ. In contrast, the minor frequent allele in some SNPs at *NRN1*,^{79,80} *TH*⁸⁵ and *ZNF804A*^{86,87} showed a protective effect: patients who were carriers had higher IQs. Two studies specified that the relationship between genetic variants and IQ was conditioned by the type of IQ. Donohoe and

Table 5 (part 1 of 2): Studies exploring different candidate genes and IQ in patients with schizophrenia

| Gene | Polymorphism | Study | Design | Country | Ancestry* | Participants, <i>n</i> | | IQ measure | Mean IQ \pm SD | | Association between polymorphism and IQ in patients with SSD |
|---|--|--|-----------------|----------------------|--|------------------------|------------------|------------|--------------------|--------------------|--|
| | | | | | | Patients | Healthy controls | | Patients | Healthy controls | |
| <i>5HT1A-R</i> | -1019 | Bosia et al. ⁵⁹ (2011) | Cross-sectional | Italy | NA | 118 (schizophrenia) | NA | WAIS | 83.46 \pm 12.54 | NA | No |
| <i>AKT1</i> | rs2494732 | Van Winkel et al. ⁶⁰ (2011) | Case-control | Netherlands, Belgium | Caucasian | 611 (NAP) | 590 | WAIS | 94.6 \pm 16.5 | NA | No |
| <i>ANK3</i> | rs1938526 | Cassidy et al. ⁶¹ (2014) | Cross-sectional | Canada | 102 Caucasian, 71 Other | 173 (FEP) | NA | WAIS | 92.6 \pm 15.7 | NA | Yes |
| <i>APOE</i> | rs7412, rs429358 | Vila-Rodriguez et al. ⁶² (2017) | Case-control | Canada | 60 Caucasian, 13 Asian, 13 Other 60:13:13 (69.8% Caucasian) | 86 (FEP) | 39 | NAART† | 100.45 \pm 8.01 | 107.54 \pm 6.75 | No |
| <i>CNNM2</i> | rs7914558 | Rose et al. ⁶³ (2014) | Case-control | Ireland | NA | 400 (SSD) | 160 | WAIS† | 91.23 \pm 18.39 | 121.4 \pm 14.6 | No |
| <i>CPLX2</i> | rs6868608, rs2443541, rs2243404, rs4242187, rs10072860, rs4868539, rs1366116, rs3892909, rs3822674, rs56934064 | Begemann et al. ⁶⁴ (2010) | Case-control | Germany | Caucasian | 1071 (SSD) | 1079 | MWT-B | NA | NA | No |
| <i>CSMD1</i> | rs10503253 | Donohoe et al. ⁶⁵ (2013) | Case-control | Ireland | Caucasian | 387 (SSD) | 205 | WAIS† | 89.74 \pm 17.46 | 118.3 \pm 13.89 | Yes |
| <i>FKBP5</i> | rs1360780, rs9470080, rs4713902, rs9394309 | Green et al. ⁶⁶ (2015) | Case-control | Australia | 98% Caucasian | 617 (SSD) | 659 | WTAR† | 97.49 \pm 15.04 | 105.47 \pm 10.67 | No |
| <i>FOLH1</i> | rs202676 | Zink et al. ⁶⁷ (2020) | Case-control | United States | Caucasian and African American | 57 (FEP) | 65 | HART | 100.7 \pm 10.6 | 104.3 \pm 10.6 | Yes |
| <i>GRIN2A, GRIN2B, GRIN3A, GRM1, GRM3, GRM4, GRM5, GRM7, GRM8</i> | 43 SNPs | Chaumette et al. ⁶⁸ (2020) | Cohort | Canada | Caucasian | 148 (FEP) | NA | WAIS | 92.8 \pm 15.4 | NA | Yes (only rs1396409 in <i>GRM7</i>) |
| <i>GRM5</i> | rs60954128, rs3824927 | Matosin et al. ⁶⁹ (2018) | Case-control | Australia | Caucasian | 249 (schizophrenia) | 261 | WASI† | 102.69 \pm 13.94 | 118.01 \pm 10.26 | Yes (only rs3824927) |
| <i>HPS4</i> | rs4822724, rs61276843, rs9608491, rs713998, rs2014410 | Kuratomi et al. ⁷⁰ (2013) | Case-control | Japan | East Asian | 240 (schizophrenia) | 240 | JART† | 92.4 \pm 10.4 | 103.4 \pm 10.7 | No |
| <i>IL1B</i> | rs16944 | Fatjó-Vilas et al. ⁷¹ (2012) | Case-control | Spain | European | 48 (schizophrenia) | 46 | WAIS† | 89.04 \pm 15.27 | 107.81 \pm 12.81 | No |
| <i>LOC100128714</i> | rs4906844 | Bakken et al. ⁷² (2011) | Case-control | Norway | Caucasian | 208 (SSD) | 368 | WASI† | 103.4 \pm 14.0 | 113.5 \pm 9.7 | No |
| <i>MHC, TCF4, NRG1</i> | rs6904071, rs13219354, rs3131296, rs6932590, rs9960767, rs12807809 | Walters et al. ⁷³ (2013) | Case-control | Germany | Caucasian | 342 (schizophrenia) | 2244 | WAIS† | 102.2 \pm 18.0 | 113.76 \pm 14.3 | Yes (only rs6904071 in <i>MHC</i>) |
| <i>MIR137</i> | rs1625579 | Green et al. ⁷⁴ (2013) | Case-control | Australia | Australian | 617 (SSD) | 764 | WTAR† | 97.49 \pm 15.04 | 105.47 \pm 10.67 | Yes (only together with negative symptoms) |
| <i>NOS1</i> | rs6490121 | Donohoe et al. ⁷⁵ (2009) | Case-control | Ireland | Caucasian | 349 (SSD) | 230 | WAIS† | 91.53 \pm 18.2 | 122.93 \pm 15.13 | Yes (only for verbal IQ) |

Table 5 (part 2 of 2): Studies exploring different candidate genes and IQ in patients with schizophrenia

| Gene | Polymorphism | Study | Design | Country | Ancestry* | Participants, <i>n</i> | | IQ measure | Mean IQ ± SD | | Association between polymorphism and IQ in patients with SSD |
|----------------|---|---|--------------|---------------|---|------------------------|------------------|------------|----------------|------------------|---|
| | | | | | | Patients | Healthy controls | | Patients | Healthy controls | |
| <i>NOS1</i> | rs6490121, rs3782206 | Zhang et al. ⁷⁶ (2015) | Case-control | China | East Asian | 580 (schizophrenia) | 720 | WAIS† | 95.99 ± 14.67 | 106.49 ± 13.99 | No |
| <i>NRG1</i> | rs2439272, rs6988339 | Anarloo et al. ⁷⁷ (2020) | Case-control | Iran | Asian | 276 (schizophrenia) | 193 | WAIS† | 74.35 ± 11.07 | 105.19 ± 7.25 | Yes |
| <i>NRGN</i> | rs12807809, rs12278912 | Ohi et al. ⁷⁸ (2013) | Case-control | Japan | East Asian | 157 (schizophrenia) | 257 | WAIS† | NA | NA | Yes (only for the diplotype) |
| <i>NRN1</i> | 19 SNPs | Chandler et al. ⁷⁹ (2010) | Case-control | Australia | Caucasian | 336 (schizophrenia) | 172 | SILS† | 89.9 ± 14.2 | 108.2 ± 8.4 | Yes (for rs1475157, rs9405890) |
| <i>NRN1</i> | 11 SNPs | Fatjo-Vilas et al. ⁸⁰ (2016) | Case-control | Spain | Caucasian | 697 (SSD) | 668 | WAIS† | 89.02 ± 15.37 | 99.48 ± 13.64 | Yes (for the haplotype rs9763180, rs1048432, rs4960155, rs9379002, rs9405890, rs1475157, before statistical correction) |
| <i>OXTR</i> | rs2254298, rs53576, rs115324487 | Montag et al. ⁸¹ (2012) | Case-control | Germany | Caucasian | 145 (schizophrenia) | 145 | MWT-B† | 103.96 ± 13.5 | 108.96 ± 13.4 | No |
| <i>OXTR</i> | rs143908202, rs150746704, rs115324487, rs61740241 | Veras et al. ⁸² (2018) | Case-control | United States | Caucasian, Hispanic, African American and Other | 48 (SSD) | 25 | WAIS† | 84.05 ± 11.75 | 102.9 ± 15.3 | Yes (only for nonverbal IQ) |
| <i>S100B</i> | rs2839357, rs1051169, rs9722 | Zhai et al. ⁸³ (2012) | Case-control | China | East Asian | 434 (schizophrenia) | 412 | WAIS† | 97.13 ± 14.87 | 108.52 ± 13.89 | No |
| <i>ST8SIA2</i> | rs4586379, rs2035645, rs4777974, rs3784735 | Fullerton et al. ⁸⁴ (2018) | Case-control | Australia | 88.1% European, 3.5% Asian, 8.4% Unknown | 281 (SSD) | 172 | WASI† | 104 | 119 | No |
| <i>TH</i> | rs10770141 | Horiguchi et al. ⁸⁵ (2014) | Case-control | Japan | East Asian | 132 (schizophrenia) | 282 | WAIS† | 103.75 ± 11.15 | 106.9 ± 8.7 | Yes |
| <i>ZNF804A</i> | rs1344706 | Walters et al. ⁸⁶ (2010) | Case-control | Ireland | Caucasian | 297 (schizophrenia) | 165 | WAIS† | 88.0 ± 16.26 | 122.26 ± 13.83 | Yes (only for high IQ) |
| <i>ZNF804A</i> | rs1344706 | Chen et al. ⁸⁷ (2012) | Case-control | China | East Asian | 531 (schizophrenia) | 442 | WAIS† | 97.09 ± 14.72 | 109.50 ± 11.88 | Yes (only for high IQ) |

FEP = first episode of psychosis; HART = Hopkins Adult Reading Test; JART = Japanese version of the National Adult Reading Test; MWT-B = Mehrfachwahl-Wortschatz Test B; NA = not available; NAART = North American Adult Reading Test; NAP = non-affective psychosis; SD = standard deviation; SILS = Shipley Institute of Living Scale test; SNP = single nucleotide polymorphism; SSD = schizophrenia spectrum disorder; WAIS = Wechsler Adult Intelligence Scale; WASI = Wechsler Abbreviated Scale of Intelligence; WTAR = Wechsler Test of Adult Reading.

*Terminology taken from the original articles.

†Patients had significantly lower IQs than healthy controls.

colleagues⁷⁵ found that carriers of the risk genotype in rs6490121 (GG) at *NOS1* had lower verbal IQs (both patients and controls), but full IQs were not significantly different. As well, some rare variants at *OXTR* demonstrated a specific link with low nonverbal IQ.⁸² Thirteen studies obtained nonsignificant results.^{59,60,62-64,66,70-72,76,81,83,84}

Genome-wide association studies

We included 6 GWASs in the review, of which 2 were cross-sectional and 4 had a case-control design (Table 6). Two studies explored SNPs and 4 searched CNVs. One of the SNP studies (50%) found no significant associations with patient IQ,⁸⁸ but the other study⁸⁹ reported 2 SNPs that were associated with patient IQ. The risk alleles were related to lower

global IQ for the 2 SNPs located at genes *CHD7* and *GATAD2A*,⁸⁹ specifically, the risk allele in rs6984242 (*CHD7*) was the most strongly associated with low verbal IQ.

From the remaining GWASs exploring CNVs, all reported significant associations were with low IQ. Martin and colleagues⁹¹ found that patients with large (> 500 kb) and rare (< 1% frequency) deletions had lower IQs than those without such polymorphisms. Similarly, Lowther and colleagues³⁵ observed that patients with pathogenic CNVs showed lower IQs, in contrast to patients with average IQs, who had the lowest yield of pathogenic CNVs. Derks and colleagues⁹⁰ identified 14 CNVs, mostly at chromosome 15q11.2 (related to intellectual disability), after studying patients who had schizophrenia and IQ scores below 70. Finally, Hubbard and colleagues⁹² found that

Table 6: Overview of genome-wide association studies related to IQ and schizophrenia

| Type of polymorphism | Study | Design | Country | Ancestry* | Participants, <i>n</i> | | IQ measure | Mean IQ \pm SD | | Findings |
|----------------------|-------------------------------------|-----------------|----------------|-----------|------------------------|------------------|------------|-------------------|--------------------|---|
| | | | | | Patients | Healthy controls | | Patients | Healthy controls | |
| SNP | LeBlanc et al. ⁸⁸ (2012) | Case-control | Norway | European | 190 (SSD) | 353 | WASI | NA | NA | No significant association with IQ |
| SNP | Whitton et al. ⁸⁹ (2016) | Case-control | Ireland | NA | 670 (SSD) | 330 | WTAR | 90.29 \pm 18.08 | 119.81 \pm 15.57 | rs6984242 (<i>CHD7</i>) and rs2905426 (<i>GATAD2A</i>) associated with IQ |
| CNV | Derks et al. ⁹⁰ (2013) | Case-control | United Kingdom | Caucasian | 64 (schizophrenia) | NA | WAIS | NA | NA | 14 CNVs related to low IQ at chromosomes 15q11.2 and 22q11.21 |
| CNV | Martin et al. ⁹¹ (2014) | Case-control | Australia | Caucasian | 82 (schizophrenia) | 50 | WASI† | 86.57 \pm 16.16 | 116.44 \pm 11.58 | Large, rare deletions related to lower IQ in patients |
| CNV | Lowther et al. ⁹⁵ (2017) | Cross-sectional | Canada | Caucasian | 546 (SSD) | NA | NA | NA | NA | Pathogenic CNVs related to lower IQ |
| CNV | Hubbard et al. ⁹² (2021) | Cross-sectional | United Kingdom | Caucasian | 875 (SSD) | NA | WAIS | NA | NA | CNV carriers with schizophrenia had lower IQ |

CNV = copy number variant; NA = not available; SNP = single nucleotide polymorphism; SSD = schizophrenia spectrum disorder; WAIS = Wechsler Adult Intelligence Scale; WASI = Wechsler Abbreviated Scale of Intelligence; WTAR = Wechsler Test of Adult Reading.

*Terminology taken from the original articles.

†Patients had significantly lower IQs than healthy controls.

patients carrying CNVs related to SSD showed significantly lower IQs than noncarriers.

Discussion

This was, to our knowledge, the first systematic review to analyze current evidence related to the genetic association between SSD and IQ. We summarized 55 studies, some of which found that variability in several genes was significantly related to SSD and IQ in different directions. At the trait level, the results were consistent in showing lower estimated IQ in patients with SSD compared to healthy controls, corresponding to findings from other reviews and meta-analyses.^{93–95} Taken together, these findings show a possible common biological correlate between the 2 traits, indicating that IQ is a strong candidate endophenotype for SSD. Our review synthesizes the current data emerging from a line of research that has yielded heterogeneous results from diverse study strategies. For this reason, we believe that the present work provides relevant information that can lead researchers to select lines of investigation with the most promising evidence. Our results point to the study of novel genes such as *NRN1*, *ZNF804A*, *CHD7* and *GATAD2A*, instead of others that have been more traditionally studied (*COMT*, *BDNF* and *DTNBP1*) but have not been supported by results from GWASs.

COMT

The most frequently studied polymorphism was Val158Met (rs4680), located at *COMT*. This gene encodes the enzyme catechol-*O*-methyltransferase (COMT), which degrades catecholamines, including dopamine, and helping to maintain

appropriate levels of this neurotransmitter, particularly in the prefrontal cortex.⁹⁶ The Val158Met polymorphism leads to a substitution of valine with methionine, in which the Val allele results in increased enzymatic activity of COMT, which in turn reduces dopamine concentrations.⁹⁷ Some studies described here established that patients with the Val genotype showed lower IQs than Met carriers,^{43–45} but others did not replicate this finding.^{39–42} The possible IQ deficit in Val carriers might be explained by a dopamine reduction in the prefrontal cortex associated with this variant, which, in turn, is linked to worse performance in terms of executive function and working memory.⁹⁸ Moreover, a study on intellectual disability suggested that Val158Met might contribute to intelligence by affecting white matter architecture in the prefrontal lobe and hippocampal formation.⁹⁹

This discrepancy in findings could be the result of differences when controlling for mediating variables such as medication and type of intelligence. Rebollo-Mesa and colleagues⁴³ noted that Val carriers had lower verbal IQs, but showed no differences in performance IQ, and this effect was exclusive for patients who were taking high doses of antipsychotics. This finding indicates that the Val158Met polymorphism could modulate the effects of antipsychotics on verbal IQ, in which carriers of the risk allele would be more susceptible to the deterioration of verbal skills as a result of medication.¹⁰⁰ This corresponds with the findings of Schacht,¹⁰¹ who stated that this same polymorphism was key in identifying patients who were most likely to respond adequately to dopaminergic drugs. For clinical practice, these outcomes suggest that there is a subgroup of SSD patients with higher genetic risk of cognitive decline who need long-term follow-up.

Further research into the Val158Met polymorphism must explore possible interactions with other SNPs, such as rs1801133 at *MTHFR*, because these interactions may influence the expression of *COMT*.⁴⁵ In fact, it has been demonstrated that polymorphisms in these 2 genes may be associated with IQ, especially because the *MTHFR*-T allele decreases the beneficial role of the *COMT*-Met allele in patients with schizophrenia.¹⁰¹

BDNF

All included studies on the *BDNF* gene analyzed the Val66Met polymorphism, probably because of its demonstrated link to schizophrenia¹⁰² and cognitive processes.¹⁰³ This gene encodes brain-derived neurotrophic factor (BDNF), a neurotrophin that has a relevant role in neurodevelopment, synapse regulation and synaptic plasticity.¹⁰⁴ Variations in this gene may lead to alterations in the BDNF protein that could cause impaired brain development and synapse and neuroplasticity failures, which have been associated with schizophrenia.^{104,105} The results found in this review related to the Val66Met polymorphism were controversial. Chung and colleagues⁴⁷ and Lu and colleagues⁴⁸ established that patients with SSD who were Met carriers had lower IQs than those who were Val carriers. This finding corresponded with previous research indicating that the *BDNF*-Met allele was associated with lower IQ in healthy women.¹⁰⁶

The Val66Met polymorphism is believed to contribute to the etiology of SSD by affecting brain morphology as a result of lower levels of BDNF: Met allele carriers show reductions in the dorsolateral prefrontal cortex, caudate nucleus and frontal grey matter volume.^{107–109} The decreased secretion of BDNF caused by Val–Met substitution may also alter synaptic plasticity and neurodevelopment,¹⁰⁵ which could influence cognition by disrupting the learning process.¹⁰⁴ However, 3 other studies included in this review found no association between the Val66Met polymorphism and IQ in people with SSD.^{46,49,50} Once again, the different findings might depend on genetic variability in *BDNF* between populations, because a significant association was found only in individuals from South Korea and China. This finding was in line with previous literature reporting a higher frequency of the Met allele in the Asian population;¹¹⁰ future studies must explore the potential differential role of the Val66Met polymorphism in patients with SSD from different genetic backgrounds. Moreover, the association of Val66Met with IQ was established only for full IQ and verbal IQ estimated by the WAIS^{47,48} but not with premorbid IQ assessed using the NAART questionnaire.⁴⁹ For this reason, Val66Met could be exclusively related to some types of IQ.

DTNBP1

Some associations were reported between SNPs at *DTNBP1* and IQ in patients with SSD. This gene encodes the dysbindin-1 protein, which plays a relevant role in neurotransmission and neurodevelopment.¹¹¹ Dysbindin-1 has been found in presynaptic and postsynaptic locations in several brain areas of interest in schizophrenia, including the hippocampus, the pre-

frontal cortex and the midbrain.^{112,113} Because dysbindin-1 interacts with different proteins involved in the release of neurotransmitters, its alteration could affect synaptic homeostasis.⁸³ In all studies with significant results, the risk allele was related to lower IQ, including the C allele in rs2619539,⁵⁵ the T allele in rs760761,⁵³ the G allele in rs2619522⁵³ and the A allele in rs3213207.⁵⁵ Furthermore, a risk haplotype that included 2 of the above SNPs (rs2619522 and rs760761) was associated with a greater decline in IQ in patients with SSD.⁵¹ The mechanism responsible for this association is unknown, but these polymorphisms might influence intelligence by reducing *DTNBP1* expression in the prefrontal cortex, hippocampus and midbrain,^{111,112} thus affecting the glutamatergic system.¹¹³

However, other studies did not find this association,^{52,54} possibly because of the great variety of SNPs analyzed. In addition, although most studies considered patients in the early stages of SSD, Hashimoto and colleagues⁵⁴ analyzed a sample with chronic SSD, which may have affected the results: changes in gene expression have been described depending on the clinical stage of the disorder.¹¹⁴ Similarly, the discrepancies found may have been a consequence of genetic variance in *DTNBP1* between populations,^{113,115} because the only study with Asian participants had negative results.

TCF4

Few studies have explored the effect of genetic variability in *TCF4* on IQ and SSD. *TCF4* encodes transcription factor 4, a basic helix–loop–helix transcription factor. *TCF4* is widely expressed in the early human embryo and might be relevant for nervous system development¹¹⁶ because of its role in neural proliferation and differentiation.¹¹⁷ Disruptions in this gene are associated with neurodevelopmental disorders that occur with intellectual disability, such as Pitt–Hopkins syndrome.¹¹⁶ However, this review found insufficient evidence to confirm a relationship between *TCF4* variability and IQ in patients with SSD. A single study obtained significant findings,⁵⁷ in which carriers of the minor allele in rs2958182 (A) had lower IQs than noncarriers. Lennertz and colleagues⁵⁶ found that patients with SSD carrying the risk allele (C) of rs9960767 had worse memory impairment, and Albanna and colleagues⁵⁸ observed that the risk allele was related to deficits in the reasoning cognitive domain. Therefore, *TCF4* polymorphisms could be linked to specific cognitive domains rather than general cognition, but further studies are needed to understand their role in the pathophysiology of SSD.

Other candidate genes

Among the results of other candidate genes, *NRN1* and *ZNF804A* showed the strongest links with IQ in patients with SSD. The *NRN1* gene encodes a protein from the neurtin family and is expressed in both embryonic development¹¹⁸ and the adult brain.¹¹⁹ It plays a role in neuronal differentiation, synapse formation and maturation, and synaptic plasticity.^{120,121} Because of these functions, it is believed that variations of this gene could confer risk for the

disorder and for neurocognitive alterations.⁸⁰ Two different studies observed that a haplotype (rs1475157 and rs9405890) at *NRN1* was related to IQ in patients with SSD.^{79,80} Chandler and colleagues⁷⁹ reported that the SNPs rs1475157 and rs9405890 had a selective influence on fluid intelligence, because carriers of the GA haplotype had lower fluid intelligence scores on both premorbid and current IQ tests. As well, variability in rs1475157 and rs9405890 was related to age at onset, which in turn modulated the long-term cognitive course of patients with SSD.¹²² Although these findings must be replicated, research into *NRN1* variations could help to identify a subgroup of patients at increased risk of cognitive impairment.

Two other studies observed that the risk allele (A) in rs1344706, located at *ZNF804A*, was associated with high IQ in patients with schizophrenia.^{86,87} Walters and colleagues⁸⁶ clarified that although patients carrying this allele had higher IQs and fewer cognitive deficits than noncarriers, they still showed cognitive impairments compared to healthy participants. This polymorphism might be implicated specifically in SSD because it has been more frequently identified in patients with the disorder,^{8,123,124} and it has been related to higher schizotypy scores in healthy individuals.¹²⁵ Overall, these findings agree on the value of the rs1344706 polymorphism as a potential genetic marker for risk of psychosis. The specific function of *ZNF804A* is still unknown, but it encodes a zinc finger binding protein, a type of protein that participates in diverse roles, such as binding to DNA, transcriptional regulation and DNA–protein interactions.^{126,127} This gene is expressed in the fetal and adult human brain, including the medial temporal lobe, the dorsolateral prefrontal cortex, the hippocampus and the amygdala.^{128–130} A plausible hypothesis is that the risk allele in rs1344706 may be related to SSD by affecting the expression of *ZNF804A* and other genes relevant for neurodevelopment,^{128–130} and by disturbing brain connectivity.¹³¹

Genome-wide association studies

In this review, *COMT*, *BDNF* and *DTNBP1* — the most frequent candidates explored in relation to IQ in patients with SSD — were not associated with such phenotypes using a GWAS strategy. There may be different reasons for the inconsistency of these results. First, because the 2 GWASs exploring SNPs included in the present review assessed patients with SSD,^{88,89} clinical heterogeneity could have diminished the statistical power to detect the effect of such genes.¹³² Moreover, their sample sizes were small, with limited statistical power, which could have interfered in the identification of genetic variants related to the traits of interest. Another plausible explanation is that the aforementioned genes (*COMT*, *BDNF* and *DTNBP1*) do not confer risk for SSD, which would be consistent with the larger GWASs in schizophrenia to date.^{8,9,133} Instead, other less explored common variations may better explain the genetic correlation between SSD and IQ reported by different GWAS meta-analyses with samples above 100 000 individuals. The studies by Hagenaars and colleagues,²⁸ Savage and colleagues²⁹ and the

Brain Consortium¹³⁴ have described substantial evidence of pleiotropy between schizophrenia and cognition, in which lower IQ¹³⁴ and slower reaction²⁸ time were genetically correlated with the disorder. Regarding intelligence, Smeland and colleagues¹³⁵ identified 75 distinct genomic loci that may underlie the genetics overlapping with schizophrenia, and gene set analysis suggests that these loci are implicated in neurodevelopment, synaptic integrity and neurotransmission. Future studies are needed that focus on these candidate loci to delve into the biological processes that might lead to the clinical and cognitive characteristics of patients with SSD. Several authors have suggested that GWASs with large samples could improve phenotypic characterization by establishing stricter inclusion criteria.^{132,136,137} Furthermore, candidate gene studies can provide interesting insights by including homogeneous samples with similar symptoms and clinical manifestations among participants, focusing on unravelling the neurobiological basis of behaviour.

Otherwise, recent GWASs have also highlighted the involvement of epigenetic mechanisms involved in SSD and IQ. Whitton and colleagues⁸⁹ explored a list of genes that are chromatin modulators of gene expression and candidate genes for schizophrenia risk. They found that 2 SNPs — 1 in *CHD7* and 1 in *GATAD2A* — were related to lower IQ in patients with SSD. The strongest association was between rs6984242 (in *CHD7*) and verbal IQ, in which carriers of the risk allele (G) showed lower IQs. *CHD7* encodes chromodomain helicase DNA binding protein 7 (*CHD7*), which participates in the organization of chromatin, making it relevant for the regulation of gene transcription, DNA repair, replication and recombination.¹³⁸ *GATAD2A* encodes the protein GATA zinc finger domain containing 2A, a subunit of the nucleosome remodelling and histone deacetylation complex, and it represses gene expression.^{139,140} These findings indicate an interesting line of research that explores the possible involvement of genes with epigenetic regulation functions in the risk for SSD and cognitive dysfunction.

The GWASs on CNVs were consistent in showing a relationship between CNV burden and low IQ in patients with SSD.^{35,90,92,141} However, this finding should be interpreted with caution, because in a recent meta-analysis including 10 studies on patients with SSD, their unaffected relatives and unrelated controls found no evidence of an association between CNV burden and overall IQ.¹⁴² Instead, the authors observed that CNVs had greater effects on specific cognitive abilities such as memory and perceptual reasoning. The potential influence of CNVs on intellectual deficits in SSD should be confirmed in future studies with larger samples that estimate different types of IQ (e.g., verbal IQ or performance IQ).

Future directions in this line of research include analyzing the various cognitive functions within the IQ construct to investigate how genetic components affect each process separately. Future research should also improve the diversity of ancestry in the samples analyzed. Although some recent work is investigating the genetic architecture of schizophrenia in Latin American and East Asian populations,^{143,144} representation of other groups, including Africans, is still lacking.

Limitations

Despite the genetic associations between IQ and SSD described above, approximately 45% ($n = 25$) of the included studies reported an absence of such a relationship. These negative results could reflect a true lack of association but could also have been because of heterogeneity in the samples when including SSD patients with diverse diagnoses and characteristics. The effect of medication might have been another confounding factor, because not all primary studies controlled for it. The instruments used to measure IQ and the type of intelligence estimated could also have been a cause of heterogeneity. Even when the same instrument was administered (in most cases, the Wechsler Adult Intelligence Scale), some authors used the full scale and others exclusively used subscales of verbal intelligence or performance intelligence. In addition, the use of different measures makes it difficult to analyze the different cognitive functions that encompass the construct of intelligence. Furthermore, most studies excluded patients with IQs of less than 70, and because intellectual disability is related to CNV and rare mutations,³⁵ relevant genetic information could have been lost. Other major limitations of some primary studies were sample size, the lack of a control group and the majority inclusion of those of Caucasian origin, leaving aside other population groups, affecting the generalizability of results to other underrepresented populations.

Regarding the systematic review itself, its main limitation was that we did not screen grey literature, so possible unpublished negative results may not have been included. Furthermore, we found few GWASs that could replicate the findings of candidate genes with larger samples and less probability of biases. This could have been because of our strict eligibility criteria, including the selection of original studies that addressed SSD diagnosis and IQ estimation simultaneously. Therefore, large and relevant GWASs such as the review by Smeland and colleagues,¹³⁵ which combined data from separate samples (schizophrenia, bipolar disorder and general population), were excluded from our results. Our findings might have been improved by a broader search strategy in terms of eligibility criteria. Likewise, the number of studies we found for each candidate gene was limited in most cases, affecting the generalizability of the results and highlighting the need for further genetic studies that replicate previous findings. Nevertheless, the present review offered some insight into the genetic basis for SSD and IQ using a systematic methodology. In addition, because we did not establish a time limitation in our bibliographic search, we analyzed all existing evidence on this topic. Similarly, the development of a protocol and its registration before the literature search contributed to the prevention of bias in the selection of studies.

Conclusion

The association between genetic variants and IQ in patients with SSD reported in the present systematic review highlights previous findings on the polygenic nature of both intelligence and SSD. However, current evidence related to specific genes associated with IQ and SSD is inconclusive. Genes

traditionally studied, such as *COMT*, *BDNF* and *DTNBP1*, have not been confirmed using a GWAS approach. Instead, novel genes have been targeted to understand the molecular basis underlying the IQ deficit in SSD, including *NRN1*, *ZNF804A*, *CHD7* and *GATAD2A*. Overall, our results support a neurodevelopmental hypothesis for SSD, because there is evidence of genetic risk factors that predispose individuals to both low IQ and risk for psychosis. In addition, results for IQ deficits in patients with SSD compared to healthy individuals, and for genetic variants associated with IQ and SSD, suggest that IQ is a valid endophenotype for SSD. Therefore, susceptibility to cognitive deficits might be present from brain development and would not be only a consequence of the disease. Therefore, IQ estimation might help to detect a subgroup of individuals at risk for psychosis.

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References

- Saha S, Chant D, Welham J, et al. A systematic review of the prevalence of schizophrenia. *PLoS Med* 2005;2:e141.
- American Psychiatric Association. *Diagnostic and statistical manual of mental disorders. Fifth edition*. Arlington (VA): American Psychiatric Association Publishing; 2013.
- Mayoral-van Son J, Juncal-Ruiz M, Ortiz-García de la Foz V, et al. Understanding the direct and indirect costs of a first episode of psychosis program: insights from PAFIP of Cantabria, Spain, during the first year of intervention. *Early Interv Psychiatry* 2019; 13:1182-90.
- van de Leemput J, Hess JL, Glatt SJ, et al. Genetics of schizophrenia: historical insights and prevailing evidence. *Adv Genet* 2016; 96:99-141.
- Lichtenstein P, Yip BH, Björk C, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* 2009;373:234-9.
- Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry* 2003;60:1187-92.
- Trubetskoy V, Pardiñas AF, Qi T, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* 2022;604:502-8.
- Ripke S, Neale BM, Corvin A, et al. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014;511:421-7.
- Pardiñas AF, Holmans P, Pocklington AJ, et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat Genet* 2018;50:381-9.
- Lencz T, Knowles E, Davies G, et al. Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: a report from the Cognitive Genomics Consortium (COGENT). *Mol Psychiatry* 2014;19:168-74.
- Greenwood TA, Lazzeroni LC, Maihofer AX, et al. Genome-wide association of endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia (COGS) study. *JAMA Psychiatry* 2019;76:1274-84.
- Lemvigh CK, Brouwer RM, Pantelis C, et al. Heritability of specific cognitive functions and associations with schizophrenia spectrum disorders using CANTAB: a nation-wide twin study. *Psychol Med* 2020 August 11 [Epub ahead of print]. doi: 10.1017/S0033291720002858.
- Zhang Z, Zhang R, Qin P, et al. Cognitive dysfunction and negative symptoms in patients with schizophrenia and their first-degree relatives from simplex and multiplex families. *Neuropsychiatr Dis Treat* 2018;14:3339-48.
- McCarthy NS, Badcock JC, Clark ML, et al. Assessment of cognition and personality as potential endophenotypes in the Western Australian Family Study of Schizophrenia. *Schizophr Bull* 2018; 44:908-21.
- Gur RC, Braff DL, Calkins ME, et al. Neurocognitive performance in family-based and case-control studies of schizophrenia. *Schizophr Res* 2015;163:17-23.
- Bertisch H, Mesen-Fainardi A, Martin MV, et al. Neuropsychological performance as endophenotypes in extended schizophrenia families from the Central Valley of Costa Rica. *Psychiatr Genet* 2009; 19:45-52.
- Wechsler D. *The Wechsler Adults Intelligence Scale*. San Antonio (TX): Psychological Corp.; 1997.
- Genç E, Schlüter C, Fraenz C, et al. Polygenic scores for cognitive abilities and their association with different aspects of general intelligence — a deep phenotyping approach. *Mol Neurobiol* 2021; 58:4145-56.
- Zabaneh D, Krapohl E, Gaspar HA, et al. A genome-wide association study for extremely high intelligence. *Mol Psychiatry* 2018; 23:1226-32.
- Coleman JRI, Bryois J, Gaspar HA, et al. Biological annotation of genetic loci associated with intelligence in a meta-analysis of 87,740 individuals. *Mol Psychiatry* 2019;24:182-97.
- Hill WD, Harris SE, Deary IJ. What genome-wide association studies reveal about the association between intelligence and mental health. *Curr Opin Psychol* 2019;27:25-30.
- Khandaker GM, Barnett JH, White IR, et al. A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophr Res* 2011;132:220-7.
- Kendler KS, Ohlsson H, Sundquist J, et al. IQ and schizophrenia in a Swedish national sample: their causal relationship and the interaction of IQ with genetic risk. *Am J Psychiatry* 2015;172:259-65.
- Jones P, Rodgers B, Murray R, et al. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet* 1994;344:1398-402.
- Cosway R, Byrne M, Clafferty R, et al. Neuropsychological change in young people at high risk for schizophrenia: results from the first two neuropsychological assessments of the Edinburgh High Risk Study. *Psychol Med* 2000;30:1111-21.
- Ohi K, Shimada T, Kataoka Y, et al. Intelligence decline between present and premorbid IQ in schizophrenia: Schizophrenia Non-Affected Relative Project (SNARP). *Eur Neuropsychopharmacol* 2019;29:653-61.
- Sniekers S, Stringer S, Watanabe K, et al. Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence. *Nat Genet* 2017;49:1107-12.
- Hagenaars SP, Harris SE, Davies G, et al. Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N=112 151) and 24 GWAS consortia. *Mol Psychiatry* 2016;21:1624-32.
- Savage JE, Jansen PR, Stringer S, et al. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet* 2018;50:912-9.
- Ohi K, Nishizawa D, Sugiyama S, et al. Polygenic risk scores differentiating schizophrenia from bipolar disorder are associated with premorbid intelligence in schizophrenia patients and healthy subjects. *Int J Neuropsychopharmacol* 2021;24:562-9.
- Ohi K, Sumiyoshi C, Fujino H, et al. Genetic overlap between general cognitive function and schizophrenia: a review of cognitive GWASs. *Int J Mol Sci* 2018;19:3822.
- Yang Y, Zhang L, Guo D, et al. Association of DTNBP1 with schizophrenia: findings from two independent samples of Han Chinese population. *Front Psychiatry* 2020;11:446.
- Smeland OB, Frei O, Kauppi K, et al. Identification of genetic loci jointly influencing schizophrenia risk and the cognitive traits of verbal-numerical reasoning, reaction time, and general cognitive function. *JAMA Psychiatry* 2017;74:1065-75.
- Mueller TM, Haroutunian V, Meador-Woodruff JH. N-glycosylation of GABAA receptor subunits is altered in schizophrenia. *Neuropsychopharmacology* 2014;39:528-37.
- Lowther C, Merico D, Costain G, et al. Impact of IQ on the diagnostic yield of chromosomal microarray in a community sample of adults with schizophrenia. *Genome Med* 2017;9:105.
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
- The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. Geneva, Switzerland: World Health Organization; 1992. Available: <https://apps.who.int/iris/handle/10665/37958> (accessed 2021 Nov. 23).
- Sohani ZN, Meyre D, de Souza RJ, et al. Assessing the quality of published genetic association studies in meta-analyses: the quality of genetic studies (Q-Genie) tool. *BMC Genet* 2015;16:50.
- Galderisi S, Maj M, Kirkpatrick B, et al. Catechol-O-methyltransferase Val158Met polymorphism in schizophrenia: associations with cognitive and motor impairment. *Neuropsychobiology* 2005;52:83-9.
- Ho BC, Wassink TH, O'Leary DS, et al. Catechol-O-methyl transferase Val158 Met gene polymorphism in schizophrenia: working memory, frontal lobe MRI morphology and frontal cerebral blood flow. *Mol Psychiatry* 2005;10:287-98.
- Prata DP, Mechelli A, Fu CHY, et al. Opposite effects of catechol-O-methyltransferase Val158Met on cortical function in healthy subjects and patients with schizophrenia. *Biol Psychiatry* 2009;65:473-80.

42. Wirgenes KV, Djurovic S, Sundet K, et al. Catechol O-methyltransferase variants and cognitive performance in schizophrenia and bipolar disorder versus controls. *Schizophr Res* 2010;122:31-7.
43. Rebollo-Mesa I, Picchioni M, Shaikh M, et al. *COMT* (Val 158/108Met) genotype moderates the impact of antipsychotic medication on verbal IQ in twins with schizophrenia. *Psychiatr Genet* 2011;21:98-105.
44. Green MJ, Chia TY, Cairns MJ, et al. Catechol-O-methyltransferase (*COMT*) genotype moderates the effects of childhood trauma on cognition and symptoms in schizophrenia. *J Psychiatr Res* 2014;49:43-50.
45. Kontis D, Theochari E, Fryssira H, et al. *COMT* and *MTHFR* polymorphisms interaction on cognition in schizophrenia: an exploratory study. *Neurosci Lett* 2013;537:17-22.
46. Ho B-C, Milev P, O'Leary DS, et al. Cognitive and magnetic resonance imaging brain morphometric correlates of brain-derived neurotrophic factor Val66Met gene polymorphism in patients with schizophrenia and healthy volunteers. *Arch Gen Psychiatry* 2006;63:731-40.
47. Chung S, Chung HY, Jung J, et al. Association among aggressiveness, neurocognitive function, and the Val66Met polymorphism of brain-derived neurotrophic factor gene in male schizophrenic patients. *Compr Psychiatry* 2010;51:367-72.
48. Lu W, Zhang C, Yi Z, et al. Association between *BDNF* Val66Met polymorphism and cognitive performance in antipsychotic-naïve patients with schizophrenia. *J Mol Neurosci* 2012;47:505-10.
49. Smith GN, Thornton AE, Lang DJ, et al. Hippocampal volume and the brain-derived neurotrophic factor Val66Met polymorphism in first episode psychosis. *Schizophr Res* 2012;134:253-9.
50. Abbasian S, Yoosefee S, Shahsavand-Ananloo E. Association between brain-derived neurotrophic factor gene variant (rs6265; C > T) and schizophrenia, its psychopathology and intelligence. *Eur J Psychiatry* 2021;4:207-15.
51. Burdick KE, Goldberg TE, Funke B, et al. *DTNBP1* genotype influences cognitive decline in schizophrenia. *Schizophr Res* 2007;89:169-72.
52. Donohoe G, Morris DW, Clarke S, et al. Variance in neurocognitive performance is associated with dysbindin-1 in schizophrenia: a preliminary study. *Neuropsychologia* 2007;45:454-8.
53. Zinkstok JR, de Wilde O, van Amelsvoort TAMJ, et al. Association between the *DTNBP1* gene and intelligence: a case-control study in young patients with schizophrenia and related disorders and unaffected siblings. *Behav Brain Funct* 2007;3:19.
54. Hashimoto R, Noguchi H, Hori H, et al. Association between the dysbindin gene (*DTNBP1*) and cognitive functions in Japanese subjects. *Psychiatry Clin Neurosci* 2009;63:550-6.
55. Varela-Gomez N, Mata I, Perez-Iglesias R, et al. Dysbindin gene variability is associated with cognitive abnormalities in first-episode non-affective psychosis. *Cogn Neuropsychiatry* 2015;20:144-56.
56. Lennertz L, Rujescu D, Wagner M, et al. Novel schizophrenia risk gene *TCF4* influences verbal learning and memory functioning in schizophrenia patients. *Neuropsychobiology* 2011;63:131-6.
57. Zhu X, Gu H, Liu Z, et al. Associations between *TCF4* gene polymorphism and cognitive functions in schizophrenia patients and healthy controls. *Neuropsychopharmacology* 2013;38:683-9.
58. Albanna A, Choudhry Z, Harvey PO, et al. *TCF4* gene polymorphism and cognitive performance in patients with first episode psychosis. *Schizophr Res* 2014;152:124-9.
59. Bosia M, Anselmetti S, Bechi M, et al. Effect of 5-HT1A-receptor functional polymorphism on Theory of Mind performances in schizophrenia. *Psychiatry Res* 2011;188:187-90.
60. Van Winkel R, Van Beveren NJM, Simons C. *AKT1* moderation of cannabis-induced cognitive alterations in psychotic disorder. *Neuropsychopharmacology* 2011;36:2529-37.
61. Cassidy C, Buchy L, Bodnar M, et al. Association of a risk allele of *ANKK3* with cognitive performance and cortical thickness in patients with first-episode psychosis. *J Psychiatry Neurosci* 2014;39:31-9.
62. Vila-Rodriguez F, Lang DJ, Baitz H, et al. Verbal memory improvement in first-episode psychosis *APOE*-epsilon 4 carriers: a pleiotropic effect? *Neuropsychiatr Dis Treat* 2017;13:2945-53.
63. Rose EJ, Hargreaves A, Morris D, et al. Effects of a novel schizophrenia risk variant rs7914558 at *CNNM2* on brain structure and attributional style. *Br J Psychiatry* 2014;204:115-21.
64. Begemann M, Grube S, Papiol S, et al. Modification of cognitive performance in schizophrenia by complexin 2 gene polymorphisms. *Arch Gen Psychiatry* 2010;67:879-88.
65. Donohoe G, Walters J, Hargreaves A, et al. Neuropsychological effects of the *CSMD1* genome-wide associated schizophrenia risk variant rs10503253. *Genes Brain Behav* 2013;12:203-9.
66. Green MJ, Raudino A, Cairns MJ, et al. Do common genotypes of FK506 binding protein 5 (*FKBP5*) moderate the effects of childhood maltreatment on cognition in schizophrenia and healthy controls? *J Psychiatr Res* 2015;70:9-17.
67. Zink CF, Barker PB, Sawa A, et al. Association of missense mutation in *FOLH1* with decreased NAAG levels and impaired working memory circuitry and cognition. *Am J Psychiatry* 2020;177:1129-39.
68. Chaumette B, Sengupta SM, Lepage M, et al. A polymorphism in the glutamate metabotropic receptor 7 is associated with cognitive deficits in the early phases of psychosis. *Schizophr Res* 2020 July 2 [Epub ahead of print]. doi : 10.1016/j.schres.2020.06.019 .
69. Matosin N, Newell KA, Quide Y, et al. Effects of common *GRM5* genetic variants on cognition, hippocampal volume and mGluR5 protein levels in schizophrenia. *Brain Imaging Behav* 2018;12:509-17.
70. Kuratomi G, Saito A, Ozeki Y, et al. Association of the Hermansky-Pudlak syndrome type 4 (*HPS4*) gene variants with cognitive function in patients with schizophrenia and healthy subjects. *BMC Psychiatry* 2013;13:276.
71. Fatjó-Vilas M, Pomarol-Clotet E, Salvador R, et al. Effect of the interleukin-1 β gene on dorsolateral prefrontal cortex function in schizophrenia: a genetic neuroimaging study. *Biol Psychiatry* 2012;72:758-65.
72. Bakken TE, Bloss CS, Roddey JC, et al. Association of genetic variants on 15q12 with cortical thickness and cognition in schizophrenia. *Arch Gen Psychiatry* 2011;68:781-90.
73. Walters JTR, Rujescu D, Franke B, et al. The role of the major histocompatibility complex region in cognition and brain structure: a schizophrenia GWAS follow-up. *Am J Psychiatry* 2013;170:877-85.
74. Green MJ, Cairns MJ, Wu J, et al. Genome-wide supported variant *MIR137* and severe negative symptoms predict membership of an impaired cognitive subtype of schizophrenia. *Mol Psychiatry* 2013;18:774-80.
75. Donohoe G, Walters J, Morris DW, et al. Influence of *NOS1* on verbal intelligence and working memory in both patients with schizophrenia and healthy control subjects. *Arch Gen Psychiatry* 2009;66:1045-54.
76. Zhang Z, Chen X, Yu P, et al. Evidence for the contribution of *NOS1* gene polymorphism (rs3782206) to prefrontal function in schizophrenia patients and healthy controls. *Neuropsychopharmacology* 2015;40:1383-94.
77. Ananloo ES, Yoosefee S, Karimipour M. Neuregulin1 gene variants as a biomarker for cognitive impairments in patients with schizophrenia. *Eur J Psychiatry* 2020;34:11-9.
78. Ohi K, Hashimoto R, Yasuda Y, et al. Influence of the *NRGN* gene on intellectual ability in schizophrenia. *J Hum Genet* 2013;58:700-5.
79. Chandler D, Dragovic M, Cooper M, et al. Impact of Neuritin 1 (*NRN1*) polymorphisms on fluid intelligence in schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 2010;153B:428-37.
80. Fatjó-Vilas M, Prats C, Pomarol-Clotet E, et al. Involvement of *NRN1* gene in schizophrenia-spectrum and bipolar disorders and its impact on age at onset and cognitive functioning. *World J Biol Psychiatry* 2016;17:129-39.
81. Montag C, Brockmann EM, Lehmann A, et al. Association between oxytocin receptor gene polymorphisms and self-rated 'empathic concern' in schizophrenia. *PLoS One* 2012;7:e51882.
82. Veras AB, Getz M, Froemke RC, et al. Rare missense coding variants in oxytocin receptor (*OXTR*) in schizophrenia cases are associated with early trauma exposure, cognition and emotional processing. *J Psychiatr Res* 2018;97:58-64.
83. Zhai J, Cheng L, Dong J, et al. *S100B* gene polymorphisms predict prefrontal spatial function in both schizophrenia patients and healthy individuals. *Schizophr Res* 2012;134:89-94.
84. Fullerton JM, Klauser P, Lenroot RK, et al. Differential effect of disease-associated *ST8SIA2* haplotype on cerebral white matter diffusion properties in schizophrenia and healthy controls. *Transl Psychiatry* 2018;8:21.

85. Horiguchi M, Ohi K, Hashimoto R, et al. Functional polymorphism (C-824T) of the tyrosine hydroxylase gene affects IQ in schizophrenia. *Psychiatry Clin Neurosci* 2014;68:456-62.
86. Walters JTR, Corvin A, Owen MJ, et al. Psychosis susceptibility gene ZNF804A and cognitive performance in schizophrenia. *Arch Gen Psychiatry* 2010;67:692-700.
87. Chen M, Xu Z, Zhai J, et al. Evidence of IQ-modulated association between ZNF804A gene polymorphism and cognitive function in schizophrenia patients. *Neuropsychopharmacology* 2012;37:1572-8.
88. LeBlanc M, Kulle B, Sundet K, et al. Genome-wide study identifies PTPRO and WDR72 and FOXQ1-SUMO1P1 interaction associated with neurocognitive function. *J Psychiatry Res* 2012;46:271-8.
89. Whitton L, Cosgrove D, Clarkson C, et al. Cognitive analysis of schizophrenia risk genes that function as epigenetic regulators of gene expression. *Am J Med Genet B Neuropsychiatr Genet* 2016;171:1170-9.
90. Derks EM, Ayub M, Chambert K, et al. A genome wide survey supports the involvement of large copy number variants in schizophrenia with and without intellectual disability. *Am J Med Genet B Neuropsychiatr Genet* 2013;162:847-54.
91. Martin AK, Robinson G, Reutens D, et al. Copy number deletion burden is associated with cognitive, structural, and resting-state network differences in patients with schizophrenia. *Behav Brain Res* 2014;272:324-34.
92. Hubbard L, Rees E, Morris DW, et al. Rare copy number variants are associated with poorer cognition in schizophrenia. *Biol Psychiatry* 2021;90:28-34.
93. Khandaker GM, Barnett JH, White IR, et al. A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophr Res* 2011;132:220-7.
94. de Zwart SMC, Brouwer RM, Agartz I, et al. Intelligence, educational attainment, and brain structure in those at familial high-risk for schizophrenia or bipolar disorder. *Hum Brain Mapp* 2022;43:414-30.
95. Kahn RS. On the origins of schizophrenia. *Am J Psychiatry* 2020;177:291-7.
96. Craddock N, Owen MJ, O'Donovan MC. The catechol-O-methyltransferase (COMT) gene as a candidate for psychiatric phenotypes: evidence and lessons. *Mol Psychiatry* 2006;11:446-58.
97. González-Castro TB, Hernández-Díaz Y, Juárez-Rojop IE, et al. The role of a catechol-O-methyltransferase (COMT) Val158Met genetic polymorphism in schizophrenia: a systematic review and updated meta-analysis on 32,816 subjects. *Neuromolecular Med* 2016;18:216-31.
98. Apud JA, Weinberger DR. Treatment of cognitive deficits associated with schizophrenia: potential role of catechol-O-methyltransferase inhibitors. *CNS Drugs* 2007;21:535-57.
99. Li J, Yu C, Li Y, et al. COMT val158met modulates association between brain white matter architecture and IQ. *Am J Med Genet B Neuropsychiatr Genet* 2009;150B:375-80.
100. Mata I, Arranz MJ, Staddon S, et al. The high-activity Val allele of the catechol-O-methyltransferase gene predicts greater cognitive deterioration in patients with psychosis. *Psychiatr Genet* 2006;16:213-6.
101. Schacht JP. COMT val158met moderation of dopaminergic drug effects on cognitive function: a critical review. *Pharmacogenomics J* 2016;16:430-8.
102. Gratacòs M, González JR, Mercader JM, et al. Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. *Biol Psychiatry* 2007;61:911-22.
103. Zhang XY, Chen DC, Xiu MH, et al. Cognitive and serum BDNF correlates of BDNF Val66Met gene polymorphism in patients with schizophrenia and normal controls. *Hum Genet* 2012;131:1187-95.
104. Nieto R, Kukuljan M, Silva H. BDNF and schizophrenia: from neurodevelopment to neuronal plasticity, learning, and memory. *Front Psychiatry* 2013;4:45.
105. Di Carlo P, Punzi G, Ursini G. Brain-derived neurotrophic factor and schizophrenia. *Psychiatr Genet* 2019;29:200-10.
106. Tsai SJ, Hong CJ, Yu YW, et al. Association study of a brain-derived neurotrophic factor (BDNF) Val66Met polymorphism and personality trait and intelligence in healthy young females. *Neuropsychobiology* 2004;49:13-6.
107. Pezawas L, Verchinski BA, Mattay VS, et al. The brain-derived neurotrophic factor Val66Met polymorphism and variation in human cortical morphology. *J Neurosci* 2004;24:10099-102.
108. Bath KG, Lee FS. Variant BDNF (Val66Met) impact on brain structure and function. *Cogn Affect Behav Neurosci* 2006;6:79-85.
109. Ho B-C, Andreasen NC, Dawson JD, et al. Association between brain-derived neurotrophic factor Val66Met gene polymorphism and progressive brain volume changes in schizophrenia. *Am J Psychiatry* 2007;164:1890-9.
110. Verhagen M, van der Meij A, van Deurzen PA, et al. Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity. *Mol Psychiatry* 2010;15:260-71.
111. Waddington JL, Zhen X, O'Tuathaigh CMP. Developmental genes and regulatory proteins, domains of cognitive impairment in schizophrenia spectrum psychosis and implications for anti-psychotic drug discovery: the example of dysbindin-1 isoforms and beyond. *Front Pharmacol* 2020;10:1638.
112. Weickert CS, Straub RE, McClintock BW, et al. Human dysbindin (DTNBP1) gene expression in normal brain and in schizophrenic prefrontal cortex and midbrain. *Arch Gen Psychiatry* 2004;61:544-55.
113. Numakawa T, Yagasaki Y, Ishimoto T, et al. Evidence of novel neuronal functions of dysbindin, a susceptibility gene for schizophrenia. *Hum Mol Genet* 2004;13:2699-708.
114. Ota VK, Moretti PN, Santoro ML, et al. Gene expression over the course of schizophrenia: from clinical high-risk for psychosis to chronic stages. *NPJ Schizophr* 2019;5:5.
115. Schwab SG, Knapp M, Mondabon S, et al. Support for association of schizophrenia with genetic variation in the 6p22.3 gene, dysbindin, in sib-pair families with linkage and in an additional sample of triad families. *Am J Hum Genet* 2003;72:185-90.
116. de Pontual L, Mathieu Y, Golzio C, et al. Mutational, functional, and expression studies of the TCF4 gene in Pitt-Hopkins syndrome. *Hum Mutat* 2009;30:669-76.
117. Ross SE, Greenberg ME, Stiles CD. Basic helix-loop-helix factors in cortical development. *Neuron* 2003;39:13-25.
118. Putz U, Harwell C, Nedivi E. Soluble CPG15 expressed during early development rescues cortical progenitors from apoptosis. *Nat Neurosci* 2005;8:322-31.
119. Harwell C, Burbach B, Svoboda K, et al. Regulation of cp15 expression during single whisker experience in the barrel cortex of adult mice. *J Neurobiol* 2005;65:85-96.
120. Zito A, Cartelli D, Cappelletti G, et al. Neuritin 1 promotes neuronal migration. *Brain Struct Funct* 2014;219:105-18.
121. Flavell SW, Greenberg ME. Signaling mechanisms linking neuronal activity to gene expression and plasticity of the nervous system. *Annu Rev Neurosci* 2008;31:563-90.
122. Fatjó-Vilas M, Prats C, Pomarol-Clotet E, et al. Involvement of *NRN1* gene in schizophrenia-spectrum and bipolar disorders and its impact on age at onset and cognitive functioning. *World J Biol Psychiatry* 2016;17:129-39.
123. Pardiñas AF, Holmans P, Pocklington AJ, et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat Genet* 2018;50:381-9.
124. O'Donovan MC, Craddock N, Norton N, et al. Identification of loci associated with schizophrenia by genome-wide association and follow-up. *Nat Genet* 2008;40:1053-5.
125. Soler J, Arias B, Moya J, et al. The interaction between the ZNF804A gene and cannabis use on the risk of psychosis in a non-clinical sample. *Prog Neuropsychopharmacol Biol Psychiatry* 2019;89:174-80.
126. Brayer KJ, Segal DJ. Keep your fingers off my DNA: protein-protein interactions mediated by C2H2 zinc finger domains. *Cell Biochem Biophys* 2008;50:111-31.
127. Laity JH, Lee BM, Wright PE. Zinc finger proteins: new insights into structural and functional diversity. *Curr Opin Struct Biol* 2001;11:39-46.
128. Esslinger C, Walter H, Kirsch P, et al. Neural mechanisms of a genome-wide supported psychosis variant. *Science* 2009;324:605.
129. Hill SK, Reilly JL, Keefe RS, et al. Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *Am J Psychiatry* 2013;170:1275-84.

130. Tao R, Cousijn H, Jaffe AE, et al. Expression of ZNF804A in human brain and alterations in schizophrenia, bipolar disorder, and major depressive disorder: a novel transcript fetally regulated by the psychosis risk variant rs1344706. *JAMA Psychiatry* 2014;71:1112-20.
131. Squassina A, Meloni A, Chillotti C, et al. Zinc finger proteins in psychiatric disorders and response to psychotropic medications. *Psychiatr Genet* 2019;29:132-41.
132. Manchia M, Cullis J, Turecki G, et al. The impact of phenotypic and genetic heterogeneity on results of genome wide association studies of complex diseases. *PLoS One* 2013;8:e76295.
133. The Schizophrenia Working Group of the Psychiatric Genomics Consortium. Mapping genomic loci prioritises genes and implicates synaptic biology in schizophrenia. *Nature* 2020;604:502-8.
134. The Brain Consortium. Analysis of shared heritability in common disorders of the brain. *Science* 2018;360:eaap8757.
135. Smeland OB, Bahrami S, Frei O, et al. Genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder, and intelligence. *Mol Psychiatry* 2020;25:844-53.
136. Peralta V, Cuesta MJ. Clinical models of schizophrenia: a critical approach to competing conceptions. *Psychopathology* 2000;33:252-8.
137. MacRae CA, Vasan RS. Next-generation genome-wide association studies. *Nat Rev Methods Primers* 2011;4:334-6.
138. Marfella CG, Imbalzano AN. The Chd family of chromatin remodelers. *Mutat Res* 2007;618:30-40.
139. Brackertz M, Boeke J, Zhang R, et al. Two highly related p66 proteins comprise a new family of potent transcriptional repressors interacting with MBD2 and MBD3. *J Biol Chem* 2002;277:40958-66.
140. Torchy MP, Hamiche A, Klaholz BP. Structure and function insights into the NuRD chromatin remodeling complex. *Cellular and molecular life sciences. Cell Mol Life Sci* 2015;72:2491-507.
141. Martin AK, Robinson G, Reutens D, et al. Cognitive and structural neuroimaging characteristics of schizophrenia patients with large, rare copy number deletions. *Psychiatry Res Neuroimaging* 2014;224:311-8.
142. Thygesen JH, Presman A, Harju-Seppänen J, et al. Genetic copy number variants, cognition and psychosis: a meta-analysis and a family study. *Mol Psychiatry* 2020;26:5307-19.
143. Fonseca L, Sena BF, Crossley N, et al. Diversity matters: opportunities in the study of the genetics of psychotic disorders in low- and middle-income countries in Latin America. *Revista brasileira de psiquiatria (Sao Paulo, Brazil: 1999)* 2021;43:631-7.
144. Lam M, Chen C-Y, Li Z, et al. Comparative genetic architectures of schizophrenia in East Asian and European populations. *Nat Genet* 2019;51:1670-8.