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FoxP2 and Schizophrenia: a systematic review

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ABSTRACT

Schizophrenia (SCZ) is a neurodevelopmental psychiatric disorder characterized by impaired information processing and neural circuit dysfunction. FoxP2, an ontological transcription factor, is crucial for brain development and neuronal differentiation. This systematic review explores the association between FoxP2 polymorphisms and SCZ using PRISMA guidelines to search PubMed and EMBASE. Articles were selected based on predefined criteria, and their findings were systematically evaluated. While no FoxP2 polymorphism was significantly associated with SCZ risk, specific variants showed relevance to clinical manifestations. Rs10447760 is linked to symptom severity and Body Mass Index (BMI), rs1456031 correlated with childhood parental abuse and auditory verbal hallucinations (AVH), rs2253478 is associated with poverty of speech, and rs2396753 is significantly related to reduced grey matter density (GMD) in SCZ patients. These findings suggest that FoxP2 polymorphisms may influence SCZ-related traits such as weight gain, language impairments, reduced GMD, and trauma-associated AVH. However, the limited sample sizes and scope of current studies highlight the need for further research to clarify FoxP2's role in less explored aspects of SCZ.

1. Introduction

Schizophrenia (SCZ) represents a complex psychiatric condition characterized by abnormalities in one or more of the following features: delusions, hallucinations, disorganized thinking, abnormal or peculiar motor behavior and negative symptoms (American Psychiatric Association, 2013). The onset of SCZ typically occurs in late adolescence to early adulthood, with males experiencing onset from late teens to early twenties, and females from early twenties to late thirties. With a worldwide prevalence of approximately 0.28 % (Charlson et al., 2018), SCZ is associated with significant reductions in life expectancy (Hjorthøj et al., 2017).

The etiopathology of SCZ is heterogenous and influenced by a combination of genetic and environmental factors (Bernardo et al., 2017). A substantial body of evidence has identified numerous prenatal and postnatal environmental risk factors, including in utero infections (Brown, 2011) childhood adversity (Setién-Suero et al., 2020), and substance use, particularly cannabis (Van Os et al., 2010). A dose-response relationship has been demonstrated, with heavy cannabis users facing up to a sixfold increase in the risk of developing SCZ (Zammit et al., 2002). Early trauma, whether sexual (Bebbington et al., 2011), emotional, or physical (Janssen et al., 2004) has been associated with at least a threefold increase in the risk of psychosis (Bendall et al., 2008; Thompson et al., 2013). Additionally, socioeconomic status has been shown to contribute to an increased risk of SCZ (Wicks et al., 2005). On the genetic side, twin studies, and genome-wide association studies (GIWAS) have estimated the heritability of SCZ to be around 80 % (Ripke et al., 2014; Sullivan et al., 2003). Recent research has identified over 120 specific genes, primarily expressed in excitatory and inhibitory neurons, as being associated with SCZ (Trubetskoy et al., 2022).

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However, each genetic variant contributes only a small effect to the overall aetiology of the disorder (Arnedo et al., 2015; Ripke et al., 2014).

Schizophrenia is increasingly recognized as a neurodevelopmental disorder, with disruptions occurring during critical periods of brain maturation, such as synaptic pruning and myelination. These processes play a key role in shaping grey matter density (GMD) and brain network organization (Keshavan et al., 2020). Consequently, many of the genes implicated in its pathogenesis are thought to be involved in neural development. In this context, extensive research has explored the pathological influence of FoxP2 in SCZ, given its role as a transcription factor and its regulation of a wide range of genes, most of which are associated with neurodevelopment.

FoxP2, a transcription factor belonging to the forkhead/winged-helix (FOX) family, regulates genes involved in neuronal differentiation, synaptic plasticity, and connectivity (Hickey et al., 2019). Initially identified for its association with speech and language disorders (Fisher et al., 2020; Lai et al., 2001), FoxP2 has been widely recognized as the "language gene" and proposed as a potential target for screening in developmental verbal dyspraxia (MacDermot et al., 2005). However, beyond its role in language, accumulating evidence suggests that FoxP2 is also involved in broader neurodevelopmental processes, particularly in brain regions implicated in SCZ, such as the frontal cortex, amygdala, and basal ganglia (Co et al., 2020).

Given its function as a transcription factor, variations in FoxP2 influence the expression of key genes such as moesin (MOE), involved in synaptic remodeling (Ismail et al., 2012), and DCDC2, which plays a critical role in neuronal migration and has been linked to communication impairments and altered grey matter density in SCZ patients (Jamadar et al., 2011). Additionally, FoxP2 interacts with transcription factors such as NURR1, a regulator of dopaminergic function (Kim et al., 2015), further highlighting its potential involvement in SCZ pathophysiology.

Beyond its molecular functions, genetic variations in FoxP2 have been associated with structural and functional alterations in language-related cortical regions, as seen in primary progressive aphasia (Premi et al., 2012), and with differences in cognitive and linguistic abilities in neuropsychiatric conditions (Park et al., 2014). Notably, experimental models of neuropsychiatric disorders suggest that FoxP2 dysregulation can contribute to behavioral phenotypes linked to impulsivity and cognitive dysfunction, with evidence that its restoration may modulate these effects (Rodríguez-Urgellés et al., 2022). Given its involvement in neural circuit maturation, dopaminergic signaling, and cortical development, FoxP2 may play a crucial role in the genetic and neurobiological mechanisms underlying SCZ.

This review synthesizes current evidence on the role of FoxP2 in the pathophysiology of schizophrenia (SCZ), aiming to identify key directions for future research. We hypothesize that specific noncoding polymorphisms in FoxP2 contribute to distinct symptom dimensions of SCZ—such as language disturbances, auditory verbal hallucinations, and cognitive dysfunction—by disrupting neurodevelopmental trajectories and interacting with environmental risk factors, including early-life adversity, sex, and metabolic status. To address this hypothesis, we systematically examine associations between FoxP2 single nucleotide polymorphisms (SNPs) and core clinical features of SCZ. We further explore FoxP2's involvement in cognitive domains typically impaired in SCZ, such as executive functioning and working memory. Neuroimaging findings are integrated to evaluate how FoxP2 variation may influence brain structure and connectivity, particularly within frontostriatal and corticolimbic networks. We also assess the gene's potential transdiagnostic relevance through its associations with other psychiatric conditions, including autism spectrum disorder, bipolar disorder, and major depressive disorder. Lastly, we examine gene–environment interactions, including trauma exposure, sex differences, and metabolic variables, as potential modulators of FoxP2 expression and function.

2. Methods

This systematic review has been registered in PROSPERO under the code CRD42023426951 and has been conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meeta-Analysis) criteria (Page et al., 2021).

2.1. Comprehensive search of literature

A comprehensive was conducted in two electronic databases, PubMed and EMBASE. All relevant scientific articles published in English and Spanish before February 2025 were considered for inclusion in this systematic review. The key search terms were: "schizophrenia" AND "FoxP2". More references from other articles were explored to identify further relevant studies.

2.2. Eligibility and study selection

No time restriction was applied to the search. Inclusion criteria were as follows: a) studies involving humans; b) written in English or Spanish; c) exploration of codified SNPs of the FoxP2 gene; d) investigation of a direct relationship between FoxP2 and SCZ. Exclusion criteria were a) reviews, meta-analysis, case series, case reports, commentaries, conference abstracts and posters; b) animal models; c) studies published in languages other than English or Spanish; d) lack of exploration of a direct relationship between FoxP2 and SCZ in the study results.

Two independent reviewers (G. S.-L. and P. S.-P.) conducted the literature search and assessed study eligibility after examining title and abstract. Full texts were reviewed for potentially eligible articles. Discrepancies in the selection of included articles were resolved through discussion with a third reviewer (R. A.-A.)

2.3. Study quality and risk of bias

A Risk of Bias (RoB) analysis was performed on all included studies using the Cochrane Collaboration Risk of Bias Tool (Higgins et al., 2011) available at https://www.riskofbias.info. Six domains were assessed: D1) sample size, D2) subject selection, D3) subject measurements, D4) outcome measurement and D5) selective reporting of outcomes. For each domain, studies were classified as "high," "low" or "unclear" risk of bias. "Unclear" was used when insufficient details were provided for the specific domain. Two independent reviewers (G.S.-L. and P.S.-P.) assessed the risk of bias, with disagreements resolved through discussion with a third reviewer (R. A.-A). Justifications for each rating are provided in Supplementary Table 1.

2.4. Data extraction and synthesis

To systematize the information from all included articles, a predefined Excel database was created, containing the following details for each study: a) General data: authors, year, country; b) Descriptive information: sample size (n), median age of participants, gender, mental disorder, length of illness; c) Genetic information: type of SNP; d) Psychosis risk association (YES/NO), including risk ratio (odds ratio, relative risk, etc.) if reported; e) Type of association: clinical symptomatology, illness risk, cognitive scores, language scores; f) Neuroimaging and brain structural changes related to FoxP2 expression; g) Results and conclusions. Data extraction was performed independently by G. S.-L. and P. S.-P, and discrepancies discussed and resolved with R. A.-A.

For heuristic purposes, articles were grouped according to their primary outcome into four categories: 1) studies focusing on genetic variation in the FoxP2 gene and its potential relationship to SCZ; 2) studies exploring the expression and grey matter density of FoxP2 in the brains of patients with SCZ; 3) studies investigating the association between FoxP2 and cognitive deficits or language impairment in SCZ; and

4) studies examining potential interactions between FoxP2 and other factors, such as childhood emotional abuse or Body Mass Index (BMI).

3. Results

Fig. 1 shows the flowchart of our search. Overall, we obtained 153 results, 107 in EMBASE and 46 in PubMed. After eliminating 45 duplicate studies, we applied the inclusion and exclusion criteria to 108 studies, assessing their eligibility. In total, 12 studies were selected for review, with a total number of 50 analyzed SNPs. Additional references were explored through the bibliographies of other articles, but no further relevant results were identified.

3.1. Description of included studies

The information from the included articles is summarized in Table 1. Most of the studies were conducted in Eastern countries, particularly China and Australia, with a few studies from the United States, the United Kingdom, and Spain. The publication years ranged from 2005 to 2024, with the highest number of publications in 2019 and 2022. Sample sizes varied significantly, ranging from 24 to over 2000 participants. Language restrictions did not affect the number of included studies.

Regarding the main outcome, some studies focused on genetic variations in the FoxP2 gene and its potential relationship with psychosis risk (n = 4), while others explored the expression and grey matter density of FoxP2 in the brains of patients with SCZ (n = 2). Several studies investigated the association between FoxP2 and cognitive deficits or language impairment in SCZ (n = 9). Two studies also explored potential interactions between FoxP2 and other factors, such as childhood emotional abuse or Body Mass Index (BMI). It is noteworthy that none of included studies examined the relationship between FoxP2 gene and the response to psychopharmacological treatment.

The included studies exhibited an overall low risk of bias (Fig. 2). Some studies have small sample sizes, which may raise concerns about the generalizability of their results. The main concern we identified was in the "Subject selection" domain, as most studies included predominantly male patients. There was low or no concerns regarding subject measurement and outcome measurement, with a few exceptions. One primary concern regarding outcome measurement selection was the scarcity of certain SNP variants and the loss of statistical significance after Bonferroni correction; however, these limitations were acknowledged by the authors.

3.2. FoxP2 and risk of psychosis

Four studies investigated the relationship between various FoxP2 polymorphisms and the risk of psychotic disorders (Lang et al., 2019; Rao et al., 2017; Sanjuán et al., 2005; Yin et al., 2018). Table 1 summarized each study, including the associations explored and some of the

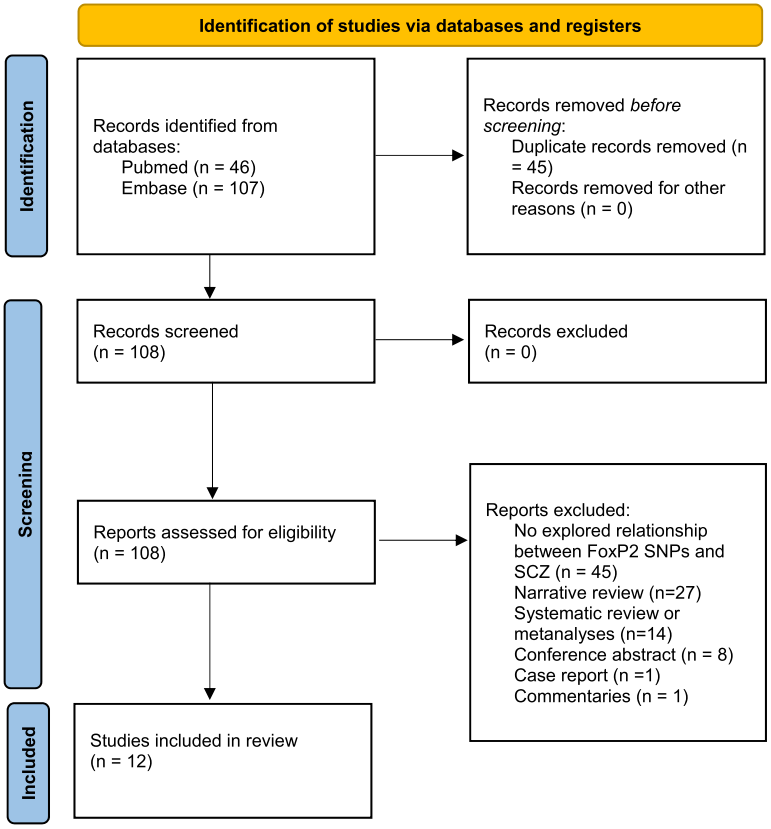

Fig. 1. Flow diagram of study selection process. Note: *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Table 1
Description of included studies.

AUTHORS	YEAR	COUNTRY	PATIENTS (n)	CONTROLS (n)	SNPs
Sanjuan et al.	2005	Spain	149 P (107m/42f)	137 HC	
			−138 SZC		Intron3a
					rs936145
			−11 SCZ-AFF		R533H
Sanjuán et al.	2006	Spain	186 SCZ (126m/60f)	160 HC	rs6466478
					rs7803667
					rs10447760
					rs7784307
					rs10276237
					rs7798050
					rs1597548
					rs2396722
					rs1358278
					rs923875
					rs17137124
					rs1852469
					rs2396753
					rs1456031
Tolosa et al.	2010	Spain	293 SCZ m	340 HC	rs7803667
					rs10447760
					rs6961558
					rs923875
					rs1597548
					rs10500038
					rs4730626
					rs717233
					rs1668335
					rs11771168
					rs1916977
					rs2396722
					rs2253478
					rs2694941
					rs1852489
					rs10255943
					rs10486026
					rs2396753
					rs17137124
					rs7799652
					rs1456029
					rs12570685
					rs1456031
					rs2396765
					rs1456021
Spaniel et al.	2010	Czech Republic	40 SCZ (18m/21f)	36 HC (17m/19f)	rs2396753
Li et al.	2013	China		1135 HC (369m/766f)	rs6466488
					rs1025010
					rs1563408
					rs6960610
					rs9969232
					rs2189015
					rs1456029
					rs17137124
			3405 P:		rs923875
			−1135 SCZ (630m/505f)		rs1358278
			−1135 DEP (483m/652f)		rs2396753
			−1135 BD (618m/517f)		rs10447760
McCarthy-Jones et al.	2013	Australia	333 P (217m/116f)	No control group	rs2253478
			−251 SCZ		rs1456031
			−42 SCZ-AFF		rs2396753
			−34 NOS		
			−6 DD		

Table 1 (*continued*)

AUTHORS	YEAR	COUNTRY	PATIENTS (n)	CONTROLS (n)	SNPs
Rao et al.	2017	China	1069 SCZ (778m/204f)	410 HC (163m/244f)	rs10447760
Yin et al.	2018	China	1405 SCZ (875m/530f)	1137 HC (630m/507f)	rs10447760
McCarthy et at.	2019	Australia	333 SSD (261m/72f)		rs2253478
					rs2396753
					rs6980093
					rs12533005
				376 C (188 f/188 m)	rs7799109
				−232 unaffected FD family members	rs17137124
				−144 HC	rs1456031
Lang et al.	2019	China	1106 SCZ (867 completed cognition assessment) (684m/183f)	404 HC (162m/242f)	rs10447760
Sanjuán et al.	2021	Spain	61 SCZ m 25m SCZ brain samples 23 RNA	18 HC m 11 HC brain samples 25 RNA	rs2396753
Yang et al.	2022	China	867 SCZ (684m/183f)	402 HC (158m/244f)	rs10447760

Abbreviations: BD: bipolar disorder; C: controls; f: female; FD: First degree; DD: delusional disorder; DEP: depressive disorder; HC: healthy controls; m: male; n: sample size; NOS: Psychosis Not Otherwise Specified; RNA: ribonucleic acid; SCZ: schizophrenia; SCZ-AFF: schizoaffective; SNP: single nucleotide polymorphism; SSD: Schizophrenia Spectrum Disorder.

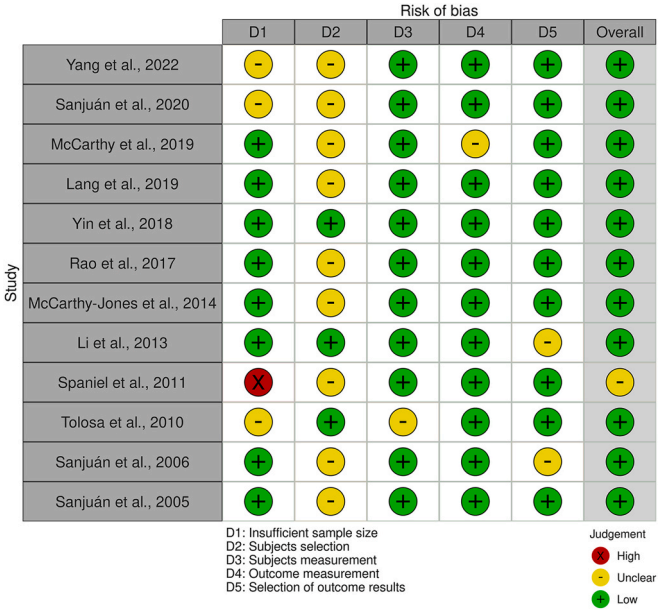

Fig. 2. Overall risk of bias of the included studies.

limitations identified. The total number of patients across the studies was 2,623, with 1684 healthy controls (HC).

Sanjuán et al. (2005) explored the association between psychotic disorder risk and the SNPs rs936145 and intron3a. They found no

significant association in a sample of 138 schizophrenia (SCZ) patients, 11 schizoaffective patients, and 137 HC. Notably, the sample included psychotic patients with active auditory hallucinations, including acute SCZ and schizoaffective patients, but not stabilized patients (Sanjuán et al., 2005).

In a similar vein, Rao et al. (2017) studied the relationship between FoxP2 rs10447760 and SCZ risk in a Han Chinese population, comparing 1069 SCZ patients with 410 HC in a case-control study. They found no significant difference in allele distribution between SCZ patients and controls (Rao et al., 2017).

Similarly, Yin et al. (2018) conducted an analysis of rs10447760 in another case-control study involving 1405 SCZ patients and 1137 HC, also in the Han population. They concluded that this SNP might not be a risk locus for SCZ susceptibility, though they acknowledged potential ethnic-geographical influences in their results (Yin et al., 2018).

Finally, Lang and colleagues (2019) examined the relationship between FoxP2 SNP rs10447760, chronic SCZ patients, and cognitive function. Like the others, they found no significant association with SCZ risk (Lang et al., 2019).

In summary, the evidence from these four studies suggests that SNPs Intron3a, rs936145, and rs10447760 are not associated with SCZ risk. However, it is worth noting that two of these studies were conducted with a Han Chinese population, while one involved a Spanish population.

3.3. FoxP2 as a modulator of clinical and cognitive function in SCZ

Three studies have explored the relationship between the FoxP2 gene and the modulation of SCZ psychopathology (Lang et al., 2019; Rao et al., 2017; Sanjuán et al., 2005), with a total sample size comprising 867 patients and 402 HC.

Sanjuán et al. (2005) investigated the association between SNPs rs936145 and intron3a and clinical symptomatology, using the Psychotic Symptom Rating Scale (PSYRATS) and the Krawiecka scale to assess auditory hallucinations and formal thought disorder (incoherence), respectively. The study yielded negative or no significant results. However, the authors acknowledged several limitations, including the lack of assessment for cognitive or language impairments and the inclusion of only patients with active auditory hallucinations, potentially influencing the outcomes (Sanjuán et al., 2005).

Rao et al. (2017) compared the FoxP2 SNP rs10447760 with clinical symptomatology in schizophrenia, as defined by the Positive and Negative Symptoms Scale (PANSS). They found a significant difference in PANSS total score, positive symptomatology, and general psychopathological scores between SCZ patients. Specifically, patients with the CC genotype had higher symptomatology and psychopathological scores than those with the CT genotype. Although the PANSS total score did not survive Bonferroni correction, differences in symptomatology and psychopathological scores remained statistically significant after correction for treatment length, BMI, gender, age, education, illness course, and age of onset. Authors discussed that their results could be misleading due to the small sample size. They also noted that the chosen patients had severe psychopathology and longer illness duration than the typical psychotic treatment-naïve patients (Rao et al., 2017).

Lang et al. (2019) studied the impact of the FoxP2 SNP rs10447760 on cognitive impairment in chronic SCZ patients by using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). In a sample of 867 SCZ patients and 402 HC they found that rs10447760 was associated with a decline in all RBANS domains, except for the visuospatial/constructional score, which remained comparable to that of HC. The most notable impairment was immediate memory, where the CT genotype group showed a significant decrease compared to the CC genotype group. It is important to note that the TT genotype was absent in this sample. The authors also highlighted the challenges of evaluating cognitive impairment in chronic SCZ patients, given the diversity of medications and illness length. Additionally, they remarked the limitations of evaluating cognitive function using the RBANS, as it only measured five cognitive domains and may not represent the full complexity of general cognitive function (Lang et al., 2019).

In summary, two of the three studies included in this systematic review found a relationship between FoxP2 gene and some aspects of the clinical psychopathology in SCZ (Lang et al., 2019; Rao et al., 2017). Specifically, the allele C of rs10447760 was related with increased psychopathology, clinical symptoms, and impaired immediate memory in SCZ patients. In contrast, the study by Sanjuán et al. (2005), which focused on different FoxP2 polymorphisms (rs936145 and intron3a), did not find a significant relationship with clinical aspects of SCZ (Sanjuán et al., 2005).

3.4. FoxP2 as modulator of language in SCZ

Six studies have investigated the relationship between language as a clinical characteristic of SCZ and FoxP2 polymorphisms(Lang et al., 2019; McCarthy et al., 2019; McCarthy-Jones et al., 2013; Sanjuán et al., 2006; Tolosa et al., 2010; Yang et al., 2022). In total, these studies included 2757 SCZ patients and 1802 HC.

Sanjuán et al. (2006) explored the association between auditory hallucinations -measured using the Manchester scale and PSYRATS- and FoxP2 SNPs in a sample of 186 SCZ patients and 160 HC. Fourteen SNPs were evaluated: rs6466478, rs7803667, rs10447760, rs7784307, rs10276237, rs7798050, rs923875, rs1597548, rs2396722, rs1358278, rs1852469, rs2396753, rs17137124 and rs1456031. Among the analyzed SNPs, only rs2396753 showed a significant association with auditory hallucinations after Bonferroni correction. Associations were observed between rs2396722, rs1358278 and speech incoherence, but these did not reach significance. Additionally, rs7803667 and rs10447760 appeared to be associated with the frequency, duration, and impact of auditory hallucinations in SCZ patients, but these associations did not survive Bonferroni correction. Notably, the study also identified two haplotypes associated with auditory hallucinations: one considered as a risk factor (rs7803667T/rs10447760C/rs923875A/rs1358278A/rs2396753A) and another considered protective (rs7803667A/rs10447760T/rs923875C/rs1358278G/rs2396753C) (Sanjuán et al., 2006).

Tolosa et al. (2010) investigated 27 FoxP2 SNPs in a sample of 293 SCZ patients and 340 HC, examining their potential association with language impairments and the intensity of auditory hallucinations. While rs2396753 and rs17137124 showed some association with auditory hallucinations, these did not remain significant after Bonferroni correction. However, rs2253478 was significantly associated with poverty of speech, but this association has not yet been replicated in independent cohorts. Additionally, haplotype analysis replicated the protective haplotype (rs7803667T/rs10447760C/rs923875A/rs2396722C/rs2396753A) against auditory hallucinations, previously identified by Sanjuán et al., in 2006. (Tolosa et al., 2010).

McCarthy-Jones et al. (2013) explored the interaction between parental childhood abuse and the risk of developing auditory verbal hallucinations (AVH) in a sample of 333 SCZ patients, 211 with history of AVH and 122 without. Their analysis focused on FoxP2 SNPs rs1456031, rs2253478 and rs2396753. They found that the C allele of rs1456031 was associated with an increased risk of AVH in patients with a history of parental emotional abuse, while it was protective in those without such history. Conversely, the TT genotype was a risk factor for AVH in patients without parental abuse, but acted as a protective factor in those who had experienced abuse. The authors acknowledged several limitations, including a small sample size, a narrow focus on parental emotional abuse without considering other trauma types, and the exclusion of non-genetic factors for AVH, such as self-blame, isolation, or anger. They suggested future research directions, including exploring FoxP2′s relationship with verbal fluency, and its role in activating frontotemporal network associated with AVH (McCarthy-Jones et al., 2013). rs2253478 This gene–environment interaction involving rs1456031 has only been reported in a single study and requires

replication to confirm its validity.

Lang et al. (2019) examined the relationship between the rs10447760 SNP and language impairment in SCZ patients and HC using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). They found that SCZ patients with the CC and CT genotypes had significantly lower language scores compared to HC with the same genotypes. However, the CT genotype group was highly imbalanced (31 SCZ patients vs. 5 HC), making the results particularly vulnerable to statistical fluctuations. Additionally, the TT genotype was absent in the sample, leaving its potential effects unexplored (Lang et al., 2019).

McCarthy et at. (2019) investigated 5 previously studied FoxP2 polymorphisms (rs2253478, rs2396753, rs7799109, rs17137124, rs1456031) and their relationship with language impairment in SCZ using the Controlled Oral Word Association Task (COWAT), the Schizotypal Personality Questionnaire (SPQ) and the Diagnostic Interview for Psychoses (DIP). The study included 333 SCZ patients, 232 unaffected first-degree relatives, and 144 HC from the Western Australian Family Study of Schizophrenia (WAFSS). No significant associations were found, which the authors attributed to the large number of statistical tests conducted (25 tests for a sample of 709 participants), leading to an increased risk of type I error (McCarthy et al., 2019).

Yang et al. (2022) explored the role of sexual dimorphism in the relationship between FoxP2 rs10447760, BMI, and cognitive deficits in SCZ. In a sample of 867 SCZ patients and 402 HC, they found that male SCZ patients with the CC genotype had better language scores compared to female SCZ patients. However, no direct association between rs10447760 and language scores was found. Interestingly, when BMI was considered, male patients with the CC genotype showed a positive association between BMI and language performance. The study noted several limitations, including unequal sample sizes between patients and HC, and between males and female groups, as well as the absence of the TT genotype in the sample, making the results somewhat inconclusive (Yang et al., 2022).

In summary, rs10447760 is the most extensively studied SNP of FoxP2 in relation to language. Some evidence suggests that the CC genotype is associated with lower language scores compared to the CT genotype (Lang et al., 2019), although more recent studies have failed to replicate this association (Yang et al., 2022). Furthermore, sex alone does not seem to modify the effect of rs10447760 on language alone, but BMI appears to interact with this SNP in male SCZ patients (Yang et al., 2022). The T allele rs10447760 is rare, and small changes in the CT or TT groups significantly impact results. Regarding rs1456031, parental abuse appears to influence the association with AVH, making the C allele a risk factor in its presence and a protective factor in its absence (McCarthy-Jones et al., 2013). Other explored SNPs have not shown significant relationship with language, likely due to small sample sizes (Sanjuán et al., 2006). Overall, most gene–environment associations reviewed here derive from single-study evidence and should therefore be interpreted with caution until further replication is achieved.

3.5. FoxP2 and neuroimaging changes in SCZ

Only two studies have investigated the relationship between FoxP2 SNPs with neuroimaging changes in SCZ (Sanjuán et al., 2021; Španiel et al., 2011).

Španiel et al. (2011) examined the association between FoxP2 rs2396753 and grey matter density (GMD) by comparing MRI images from genotyped SCZ patients and HC. Their findings revealed that SCZ patients had lower GMD than HC, particularly in the prefrontal and temporal areas, as well as in the amygdala, bilateral insular cortex, anterior cingulate cortex, bilateral premotor cortex, right somatosensory cortex, and bilateral superior lateral temporal areas. Additional regions with GMD reductions included the bilateral cerebellum, right basal ganglia, bilateral parietal lobes, and left occipital lobe. No brain areas showed increased GMD in SCZ patients. The study further classified GMD reductions according to the rs2396753 genotype, revealing that SCZ patients with the AC genotype had lower GMD than any other group (notably, there were only one SCZ CC patient, who was excluded from comparison). Interestingly, no significant differences in GMD were observed between SCZ AA group and the HC AA group (Španiel et al., 2011).

Sanjuán et al. (2021) also studied the association between rs2396753 and GMD in male SCZ patients. They compared FoxP2 expression in the prefrontal cortex (PFC) using postmortem samples from 61 genotyped SCZ patients and 18 HC, alongside neuroimaging data from 48 genotyped SCZ patients and 36 HC to assess the association between FoxP2 haplotypes and GMD reductions. Their results indicated that FoxP2 expression was reduced in the PFC of SCZ patients, with the AA group showing higher expression levels than the AC or CC group. Additionally, SCZ patients had reduced GMD in the insular, temporal, frontal and cingulate cortices, with CC SCZ patients displaying the most pronounced GMD reductions compared to AC or AA SCZ patients. Furthermore, AC SCZ patients had lower GMD than AC HC. The authors emphasized that differences in sample sizes between SCZ patients and HC, particularly in the AA and the CC genotype groups, limited the comparability of genotype effects on GMD. Moreover, the cautioned that their results should be interpreted with caution, as the rs2386753 alleles in SCZ deviated from Hardy-Weinberg equilibrium (HWE) (Sanjuán et al., 2021).

Both studies explored the same SNP, rs2396743, and reported similar results: in SCZ patients, the presence of the C allele is associated with lower GMD. The affected brain regions by this effect in both studies are nearly superposed. This pattern has been observed in two independent samples (Španiel et al., 2011; Sanjuán et al., 2021), supporting the reproducibility of this association.

3.6. FoxP2 and other mental disorders

Li et al. (2013) studied the effects of 12 different FoxP2 SNPs in four identically sized samples (1135 individuals each) comprising patients with SCZ, major depression, bipolar disorder and HC. Their findings revealed that only rs10447760 was associated with both, SCZ and DEP (Li et al., 2013). Additionally, rs2396753-an SNP previously linked to SCZ (Sanjuán et al., 2006), – was not found to be associated with SCZ in Han Chinese patients (Li et al., 2013). As observed in prior studies, small changes in the numbers of individuals carrying rare SNP variants could significantly impact the statistical significance of the results.

4. Discussion

4.1. Summary of main findings

We reviewed 12 studies examining FoxP2 polymorphisms in relation to various aspects of schizophrenia (SCZ), including risk of development, clinical psychopathology, cognitive and language-related symptoms, neuroimaging findings, and overlap with other psychiatric disorders. Our review found no evidence that any of the studied FoxP2 polymorphisms are associated with an increased risk of psychosis, despite extensive research efforts and the large number of SNPs analyzed ($n = 50$). However, FoxP2 rs10447760 has been investigated multiple times and may contribute to clinical manifestations of SCZ, as it is associated with higher psychopathological scores in affected patients. Additionally, its expression appears to be linked to other clinical factors such as sex and BMI. Nevertheless, the rarity of its T allele in the analyzed studies warrants caution in interpreting these findings. The main findings of this review—linking *FoxP2* SNPs to schizophrenia-related traits across clinical, structural, and environmental domains—are illustrated in Fig. 3.

On the other hand, the interaction between rs1456031 and parental childhood abuse in the emergency of auditory verbal hallucinations (AVH) is particularly significant, as it highlights the potential relationship between FoxP2 polymorphisms and environmental or biographical

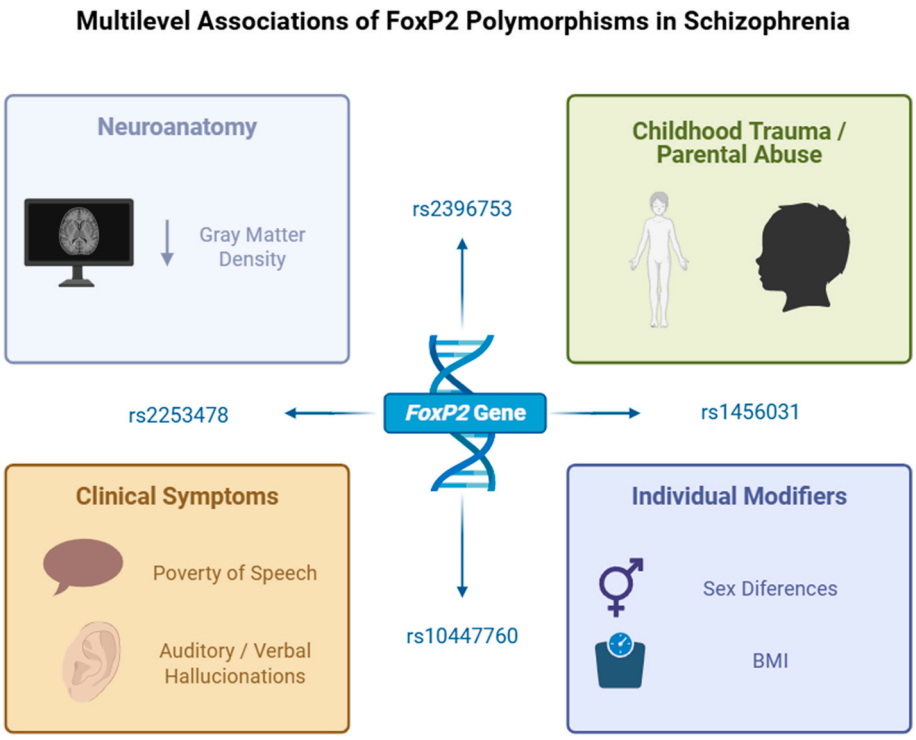

Fig. 3. Multilevel associations of FoxP2 Polymorphism in Schizophrenia.

factors in the onset of SCZ. Regarding language-related symptoms in SCZ, the only significant association identified was between rs2253478 and poverty of speech. Finally, in neuroimaging studies, the rs2396753C variant of FoxP2 appears to play a key role in the reduction of grey matter density (GMD) in SCZ patients, a well-established neuroanatomical marker of the disease.

4.2. Comparison to existing research

While the studied SNPs in our review are in noncoding regions of FoxP2, growing evidence suggests that noncoding DNA plays a crucial role in gene regulation through 3D chromatin organization. Orozco et al. (2022) highlighted how this spatial genome organization interacts with regulatory elements such as enhancers and silencers, influencing gene expression and ultimately impacting neuronal function (Orozco et al., 2022). Given that FoxP2 is a highly conserved developmental gene, its noncoding regions are essential for ensuring its timely and localized activation during neurodevelopment (Woolfe et al., 2005). These regulatory mechanisms may be particularly relevant in the context of SCZ, where disruptions in gene expression and brain maturation have been extensively reported.

In terms of neuroanatomical implications, several studies have linked FoxP2 SNPs to psychiatric and neurological disorders. As previously discussed, FoxP2 plays a key role in neurodevelopment, and alterations in its function may contribute to structural and functional abnormalities observed in SCZ. Specifically, FoxP2 has been implicated in cortico-striatal circuits, which are essential for language processing and cognitive control (Premi et al., 2012; Rodríguez-Urgellés et al., 2022), two domains frequently impaired in SCZ.

In contrast to the findings from Śpaniel et al. (2011), which linked FoxP2 rs2396753C to reduced GMD in SCZ patients, Hoogman et al. (2014) analyzed 9 SNPs in a cohort of 1301 healthy participants and found no significant association with any of the SNPs studied (Hoogman et al., 2014). However, they noted that studies involving disease cohorts, like SCZ, might have shown different results due to the potential influence of other genetic factors involved in the disease. These contrasting results highlight the complexity of understanding the role of FoxP2 in SCZ, suggesting that the gene's impact on GMD may be influenced by interactions with other genetic factors, especially in the context of psychiatric disorders.

Beyond genetic factors, environmental influences also modulate FoxP2 expression, potentially shaping vulnerability to psychotic symptoms. For example, McCarthy-Jones et al. (2013) proposed that childhood trauma may influence FoxP2 regulation, contributing to AVH by disrupting inner speech processing (McCarthy-Jones et al., 2013), reinforcing the relationship between inner speech and AVH (Upthegrove et al., 2016). However, while this relationship is well defined, its underlying mechanisms remain unclear. Specifically, the connection between FoxP2 and key stress-related brain structures, such as the hypothalamus and the pituitary gland, has not been fully explored, nor has the potential influence of stress on FoxP2 expression.

Although this gap remains, previous research has demonstrated a link between child abuse-related stress and hypothalamic-pituitary-adrenal (HPA) axis dysregulation (Kuhlman et al., 2018), as well as an association between increased baseline HPA axis activity and SCZ (Walker et al., 2008). These findings suggest a possible but yet untested pathway connecting stress, FoxP2 expression, and SCZ risk. Further research is needed to investigate whether FoxP2 interacts with stress-related pathways, particularly within the HPA axis, to better understand its role in psychosis susceptibility.

Similarly, Yang et al. (2022) examined the effect of BMI on FoxP2 expression, suggesting a broader relationship between metabolic and cognitive pathways (Yang et al., 2022). This is consistent with findings from Marioni et al. (2016), who identified an overlap between metabolic and neurological processes, including genes involved in insulin regulation (AKAP6), lipid transport and Alzheimer's disease (TOMM40), and cognitive function (TNRC6B) (Marioni et al., 2016). Although these studies do not directly link BMI to SCZ, they highlight the complex interplay between gene expression, neurodevelopment, and environmental factors that may influence psychosis risk.

4.3. Potential sources of bias

Potential sources of bias within the included studies may have influenced the interpretation of our findings. Of the 72 domain ratings assessed using the Cochrane Risk of Bias tool, 54 (75.0 %) were classified as "low risk," 17 (23.6 %) as "unclear," and only one (1.4 %) as "high risk," indicating overall acceptable methodological quality.

However, domain-specific analysis revealed important limitations. Regarding sample size (D1), 8 of 12 studies (66.7 %) were considered low risk, while 3 (25.0 %) were unclear and 1 (8.3 %) was high risk. Small samples may undermine statistical power, increase the chance of both false-positive and false-negative associations, and thus limit the reliability of links between *FoxP2* variants and schizophrenia phenotypes.

Subject selection (D2) emerged as a more consistent concern, with only 3 studies (25.0 %) rated as low risk and 9 (75.0 %) as unclear. Inadequate or poorly reported inclusion strategies—such as absence of sex stratification or unclear recruitment procedures—may have introduced selection bias, reducing generalizability.

Although most studies showed low risk in outcome measurement and reporting, the two domains above represent recurrent weaknesses. One study (Španiel et al., 2011) was classified as high risk due to its particularly small sample size. Importantly, risk of bias was systematically assessed by two independent reviewers and resolved by consensus, minimizing subjectivity in these judgments.

These findings underscore the need for future studies to implement more rigorous recruitment strategies, ensure adequate statistical power, stratify by key demographic variables, and improve transparency in methodological reporting to enhance the validity and reproducibility of genetic associations in schizophrenia research.

4.4. Strengths

This review offers a focused synthesis of an emerging area by systematically examining FoxP2 polymorphisms in schizophrenia (SCZ)—a gene extensively studied in relation to language and neurodevelopment, but rarely addressed in psychiatric genetics with this degree of specificity. The methodological approach adhered to Cochrane standards, with dual independent review and resolution of discrepancies by a third author, ensuring transparency and minimizing bias. By integrating genetic data with clinical symptomatology, neuroimaging findings, and environmental exposures, the review provides a multidimensional perspective on the potential mechanisms linking FoxP2 to SCZ. This transdiagnostic and circuit-based framework highlights current knowledge gaps and supports future interdisciplinary research. Furthermore, by distinguishing replicated from novel SNP–phenotype associations, the review refines current genetic models of SCZ, moving beyond traditional candidate gene approaches. Throughout, interpretations remain cautious, evidence-based, and contextually grounded to avoid overgeneralization.

4.5. Limitations

The primary limitation of the present review is the relatively small number of studies available on this topic (n = 12). Despite our efforts to expand the search criteria and databases, the limited number of studies highlights the need for further investigation in this field.

Another key limitation is the male-to-female ratio in the analyzed studies. While the overall incidence of SCZ does not significantly differ between sexes, some studies report a ratio of 1.4:1 (McGrath et al., 2008). In contrast, our reviewed studies presented a ratio of 1.7:1. Furthermore, some studies did not report sex differences in their methodologies. This lack of reporting could introduce potential bias in interpreting the results.

The sample size across the reviewed studies also poses a significant limitation. On average, the studies included 773 patients and 350 controls. However, many studies acknowledged that even small changes in allele frequency could dramatically affect the results, particularly for rare variants, like rs10447760T. Therefore, larger cohorts are necessary to validate these findings and improve their reliability.

Factors such as age, or length of illness were not fully explored due to the limited sample sizes. This limitation might have resulted in the failure to identify significant associations, suggesting the need for future investigations with larger datasets to explore subgroups.

A critical challenge in psychiatric genetics is the measurement of mental disorder symptomatology. Obermeier et al. (2011) pointed out that more than 60 % of high-impact studies misused the PANSS scale, recommending percent change scores over raw scores to assess symptom improvement. This methodological issue could affect the validity of the findings in the reviewed studies (Obermeier et al., 2011).

Furthermore, none of the included studies explored how non-coding SNPs influence FoxP2 expression and function. While there is evidence that non-coding DNA plays a crucial role in genome 3D structure and gene regulation (Orozco et al., 2022), no study has investigated how the SNPs reviewed here might impact the FoxP2 promoter-enhancer interactions.

Lastly, publication bias is an inherent limitation of systematic reviews and meta-analyses (Dalton et al., 2016). The tendency to publish only statistically or clinically significant results may have influenced the findings reported in the literature. Consequently, our results should be interpreted with caution.

4.6. Future perspectives

Advancing our understanding of FoxP2 *in schizophrenia (SCZ) requires a mechanistic, multidimensional research strategy. While several* FoxP2 *polymorphisms—such as rs2253478, rs1456031, and rs2396753—have been linked to specific symptom domains and neuroanatomical changes, most findings remain correlational, underpowered, and lacking replication. Functional analyses using CRISPR editing, reporter assays, and chromatin conformation mapping are needed to elucidate how noncoding variants regulate* FoxP2 *expression, particularly in SCZ-relevant brain regions.*

Multimodal neuroimaging studies can help map these variants to alterations in brain structure and connectivity, especially in frontostriatal and corticolimbic circuits. While rs2396753 has been associated with grey matter reductions, longitudinal and cross-cohort imaging data are needed to establish consistent neural signatures of FoxP2 *variation. Similarly, future studies should extend phenotypic analysis beyond positive and cognitive symptoms, incorporating underexplored dimensions such as affective, disorganized, and negative features, within dimensional and transdiagnostic frameworks.*

Gene–environment interactions also warrant further investigation. Although rs1456031 has been linked to childhood trauma, the role of FoxP2 *in mediating responses to broader stressors—including prenatal insults and adolescent adversity—remains poorly understood. Preclinical evidence suggests that* FoxP2 *is sensitive to stress signaling, implicating the hypothalamic–pituitary–adrenal (HPA) axis as a potential modulator. Future human studies should integrate biomarkers of inflammation and stress reactivity to clarify shared vulnerability mechanisms.*

Another critical gap concerns the influence of FoxP2 *on treatment response. Given its regulatory roles in dopaminergic and glutamatergic signaling, genetic variants may influence antipsychotic efficacy, side-effect profiles, or cognitive remediation outcomes. Downstream targets such as* NURR1 *and* DCDC2 *may further modulate neuroplasticity, with implications for individualized interventions.*

To address these questions, future research should harness large, diverse samples and integrative datasets—such as those from ENIGMA or the Psychiatric Genomics Consortium (PGC)—to improve statistical power, replicability, and generalizability. Emphasizing cross-cohort validation and functional annotation will be essential to delineate the role of FoxP2 *in SCZ pathophysiology and its potential as a target in precision psychiatry.*

4.7. Conclusions

We have analyzed 12 studies investigating the relationship between FoxP2 SNPs and SCZ. Out of the 50 SNPs examined, only three (rs10447760, rs1465031, and rs2396753) have shown a significant association with various aspects of the disorder. Specifically, rs10447760 is linked to clinical manifestations of SCZ and is also associated with BMI in patients with SCZ. Similarly, rs1465031 is related to AVH and parental child abuse, while rs2396753 is associated with GMD in SCZ patients. Although this review integrates promising associations between FoxP2 polymorphisms and schizophrenia-related phenotypes, the lack of consistent replication across studies limits the strength of our overall conclusions. Many of the reviewed findings—particularly those involving gene–environment interactions or cognitive endophenotypes—stem from single-study reports with modest sample sizes. As such, these conclusions should be viewed as preliminary and hypothesis-generating, pending further validation in larger and more diverse cohorts. Furthermore, numerous aspects of SCZ remain unexplored in relation to FoxP2, meaning the full extent of its involvement in the disorder has yet to be determined.

CRediT authorship contribution statement

Gabriel Salmón-Gómez: Writing – original draft, Methodology, Data curation. **Paula Suárez-Pinilla:** Writing – original draft, Supervision, Methodology, Data curation. **Esther Setién-Suero:** Writing – review & editing. **Carlos Martínez-Asensi:** Writing – review & editing, Methodology. **Rosa Ayesa-Arriola:** Writing – review & editing, Supervision, Methodology, Conceptualization.

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Declaration of competing interest

The authors declare that they have no conflicts of interest related to this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2025.07.016.

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