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TRABAJO FIN DE GRADO

RELACIÓN ENTRE POLIMORFISMOS DE FOXP2 Y LA ESQUIZOFRENIA: UNA REVISIÓN SISTEMÁTICA

RELATIONSHIP BETWEEN FOXP2 POLYMORPHISMS AND SCHIZOPHRENIA: A SYSTEMATIC REVIEW

Autor/a: GABRIEL SALMÓN GÓMEZ

Director/es: PAULA SUÁREZ PINILLA
ROSA AYESA ARRIOLA

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ABBREVIATIONS

AFF-SCZ – Schizoaffective disorder

ASD – autism spectre disorder

AVH – Auditory verbal hallucinations

BMI – Body mass index

BD – Bipolar disorder

CNS – Central nervous system

COWAT – Controlled Oral Word Association Task

DEP – Major depression disorder

DIP – Diagnostic Interview for Psychosis

GMD – Grey matter density

HT – Healthy controls

HPA – Hypothalamic-pituitary-adrenal

HWE – Hardy-Weinberg equilibrium

MR – Magnetic resonance

PANSS – Positive and Negative Symptoms Scale

PFC – Prefrontal cortex

PPA – Primary progressive aphasia

PTSD – Post-traumatic stress disorder

PSYRATS – Psychotic Symptom Rating Scale

RBANS – Repeatable Battery for the Assessment of Neuropsychological Status

RS – Reference SNP

SCZ – Schizophrenia

SNP – single nucleotide polymorphism

SPQ – Schizotypal Personality Questionnaire

WAFSS – Western Australian Family Study of Schizophrenia

ABSTRACT

Introducción: La esquizofrenia (SCZ) es una enfermedad psiquiátrica de probable origen en el neurodesarrollo. Sus síntomas están causados por alteraciones en circuitos neuronales claves en el procesamiento de la información y la codificación de estímulos. FoxP2 es un factor de transcripción ontológico en desarrollo cerebral, con un importante número de efectores en la diferenciación y maduración neuronal.

Objetivo: Explorar la relación entre polimorfismos de FoxP2 y manifestaciones de los trastornos del espectro de la SCZ.

Metodología: Revisión bibliográfica basada en PRISMA, en PubMed y EMBASE, llevado a cabo atendiendo a criterios de inclusión y exclusión. Los aspectos mas relevantes de la búsqueda fueron recogidos en una tabla.

Resultados: Ningún polimorfismo estudiado esta significativamente asociado al riesgo de desarrollar SCZ. Rs10447760 está asociado a la manifestación clínica de la enfermedad y el efecto del Índice de Masa Corporal (IMC). Rs1456031 está asociado a

los efectos que tiene el abuso paterno infantil en las alucinaciones verbales auditivas. Rs2253478 está relacionado con la pobreza del discurso. Rs2396735 está asociado significativamente a la reducción en la Densidad de Materia Gris (DMG) en el cerebro de pacientes con SCZ.

Conclusión: Ciertos polimorfismos de FoxP2 podrían mediar en manifestaciones de la SCZ como el aumento de peso, pobreza del discurso y la reducción de la densidad de la materia gris, y en los efectos del trauma en las alucinaciones auditivas verbales. Sin embargo, los trabajos revisados llaman la atención por el pequeño tamaño muestral en sus investigaciones. Los resultados del presente trabajo apuntan a la necesidad de nuevos diseños de investigación con mayores muestras y que permitan explorar la relación de FoxP2 con la SCZ en aspectos de la enfermedad escasamente estudiados.

Introduction: Schizophrenia (SCZ) is a psychiatric disease of probable neurodevelopmental origin. Its cardinal symptoms are caused by alterations in key neural circuits in information processing and stimuli coding. FoxP2 is an ontological transcription factor in brain development, with an important number of effectors in neuronal differentiation and maturation.

Objective: Explore the relationship between FoxP2 polymorphisms and manifestations of SCZ spectrum disorders.

Methodology: We performed a bibliographic search based on PRISMA, in PubMed and EMBASE, carrying out the selection according to inclusion and exclusion criteria. We synthesized the articles found in a table.

Results: No polymorphism studied is significantly associated with the risk of developing SCZ. Rs10447760 is associated with the clinical manifestation of the disease and the effect of Body Mass Index (BMI). Rs1456031 is associated with the effect of childhood parental abuse on auditory verbal hallucinations (AVH). Rs2253478 is related with poverty of speech. Rs2396735 is significantly associated with reduced Grey Matter Density (GMD) in the brain of SCZ patients.

Conclusion: Some FoxP2 polymorphisms may mediate in SCZ manifestations such as weight gain, poverty of speech, GMD reduction or trauma-related AVH. However, the small sample size of most reviewed studies points out the need of new investigation designs with bigger samples to explore the relation of FoxP2 and aspects of SCZ still poorly analysed.

Introduction

SCZ

Epidemiology

The prevalence of SCZ worldwide is around 0,28%, from 2016 data (Charlson et al., 2018), with relatively no differences in sex, localizing 70% of cases between the ages of twenty-five to fifty-five years old. Charlson et al. pointed out the lack of quality epidemiological data so, even taking very strict inclusion criteria, their result must be taken with consideration. As is represented in Figure 1, the onset of the disease is from late teens to early twenty's for men and from early twenty's to late thirty's years all for

women. The years of potential life lost because of the disease are estimated to be around 14,5±3,3 potential years lost, and an average life expectancy of 64,7±3.6 years (Hjorthøj et al., 2017).

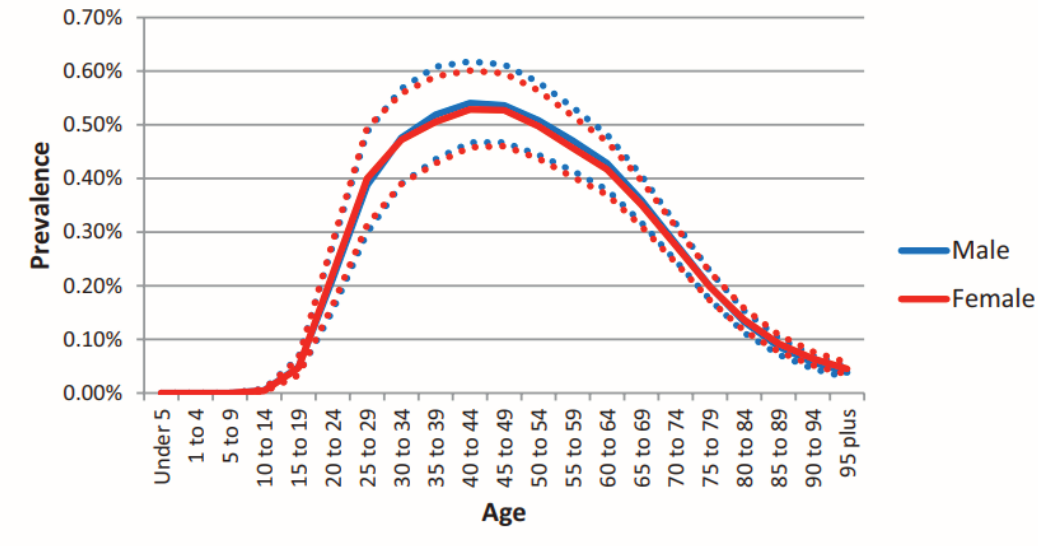

Figure 1 From Charlson et al., 2018, with 2016 data. Global mean prevalence rates (with 95% uncertainty interval) by age and sex

There is a great body of research related with the possible environmental factors that can increase the risk of SCZ (see Brown, 2011). Even before birth, we are exposed to several potential factors such as in utero infection by rubella, toxoplasma, HVS-2, influenza (Brown, 2011), that can alter the neurodevelopment; even the born season can be a risk factor and there is an increase of up to 15% in risk of developing SCZ in those born in winter or early spring (Davies et al, 2003). Nutritional factors can also influence the risk of SCZ, for example folate deficit (Goff and Coyle, 2001), iron deficit (Ben-Schachar et al., 1986), vitamin D (McGrath, 1999). A nowadays problem as it is the advanced parental age it is also a risk factor for developing SCZ (Miller et al., 2010), increasing a 10% the risk of SCZ if the parental age is greater than thirty years old.

In childhood and adulthood, we are not free of encountering some potential risk factors for SCZ. Cannabis may be the most studied one, and a dose-response relationship has been demonstrated, increasing the risk up to six times in heavy users (Zammit et al., 2002). Socioeconomic status was proposed as a risk factor as early as 1958 by Hollingshead and Redlich and confirmed in 2005 by Wicks et al. also stablishing a dose-response relationship, leading those in worse position to a high risk of SCZ. Finally, childhood trauma, whether this is sexual (Bebbington et al. 2004), emotional or physical (Janssen et al. 2004) increase at least three times the risk of psychosis.

Clinical manifestation and diagnosis

The DSM-V has stablished six (A-F) clinical criteria to diagnose SCZ (American Psychiatric Association, 2013):

A) Two (or more) of the following, each present for a significant portion of time during a **1-month period** (or less if successfully treated). At least one of these should include 1-3

    a. **Delusions**
    b. **Hallucinations**
    c. **Disorganized speech**
    d. Grossly disorganized or catatonic behavior
    e. Negative symptoms: affective flattening, alogia, or avolition

B) Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as **work, interpersonal relations, or self-care,** are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement)

C) Duration: Continuous signs of the disturbance persist for **at least 6 months.**
    a. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms.
    b. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences)

D) **Schizoaffective and major mood disorder exclusion**: Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either
    a. no major depressive or manic episodes have occurred concurrently with the active phase symptoms; or
    b. if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E) **Substance/general medical condition exclusion**: The disturbance is not attributed to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F) **Relationship to Global Developmental Delay or Autism Spectrum Disorder (ASD):** If there is a history of ASD or other communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month (or less if successfully treated).

Note that the so-called cognitive symptoms do not appear as a key feature of SCZ in the Criterion A, but Reichenberg et al. (2009) showed that between 55% and 84% of SCZ patients suffer from this symptomatology. In their paper, they defined the cognitive symptoms as neuropsychological deficits, including under this term measures of verbal memory, visual memory, executive function, attention and processing speed, language ability, sensory and motor skills, general verbal ability and visual processing.

Etiopathology

There is a vast field partially explored which try to unravel SCZ from a molecular perspective. A recent work (Trubetskoy et al., 2022) has defined 120 genes (106 protein-coding), most of them expressed in excitatory and inhibitory neurons of the central nervous system (see Figure 2). Some of these genes were:

- Ion channel: voltage-gated calcium (CACNA1C) and chloride channels (CLCN3),
- Metabotropic receptors: for glutamate (GRM1) and GABA (GABBR2), the ligand-gated NMDA receptor subunit (GRIN2A).
- Others proteins related with: endocytosis (SNAP91), synaptic organisation and differentiation (DLGAP2, LRRC4B, GPM6A, PAK6, PTPRD), modulation of chemical transmission (MAPK3, DCC, CLCN3, DLGAP2).

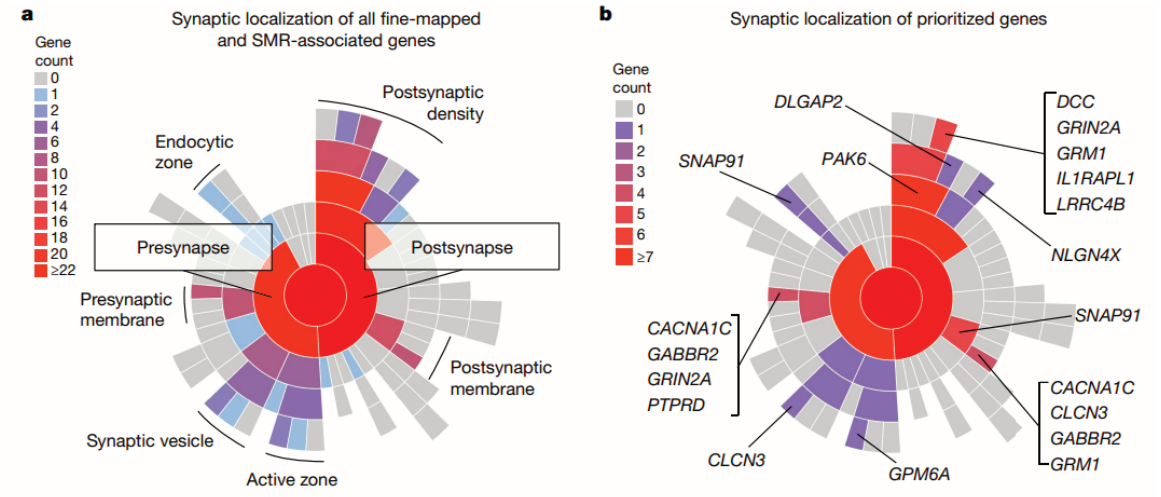

Figure 2 From Trubetskoy et al., (2022) Sunburst plots depict synaptic locations starting with the synapse (centre), pre- and postsynaptic locations in the first ring and child terms (that is, terms that are subsets of the adjacent inner ring) in subsequent rings. The number of genes in each term is indicated by the colour scheme in the legend. ***a****, FINEMAP/SMR genes are protein-coding genes tagged by at least one credible SNP identified by FINEMAP and/or associated using SMR (n = 470), of which n = 58 are SynGO-annotated, 51 to cellular components.* ***b****, Prioritized genes, of which 15 are SynGO-annotated, 14 to cellular components.*

Neural networks

SCZ is characterized as a neurodevelopmental disorder that may start at early adolescence, when the brain structure is reorganize by synaptic pruning via microglia and myelinization. During this period, the number of synapses decrease by half and there is also a decrease in gray matter volume. If these proceses are not correctly controlled, the grey matter volume loss can be too much and the resultant network aberrantly organized, both key features of SCZ.

The cognitive and negative symptoms of SCZ may be caused by an abnormal functioning of the gamma oscillations, which play a key role in cognitive abilities. Why this happens? It looks to be due to an imbalance in excitatory and inhibitory neurons. Post-mortem studies have shown a lower density of dendritic spines on pyramidal neurons, lower mRNA levels of parvalbumin and markers of other inhibitory interneuron subtypes, and lower levels of glutamate decarboxylase 67 (GAD67) mRNA and GAD67 protein, an enzyme involved in GABA synthesis. (McCutcheon et al. 2020)

Subcortical dopamine dysregulation is another core feature of SCZ, and it is involved in the creation of delusional beliefs. We are surrounded by stimuli and our brain classifies them depending on our experience based on reward prediction. Dopamine release encodes how rewarding is the stimuli and updates our cognitive models of the world. However, striatal dopamine synthesis and release capacity is higher in SCZ, leading to encode irrelevant stimuli as salient, creating a delusional belief. Here is where childhood

trauma and abuse play their role, associating stimuli with experience via a cognitive bias. (McCutcheon et al. 2020).

FoxP2

The discovery

In 1995, Vargha-Khadem et al. published a paper presenting a four-generation family (KE) of 30 members (Figure 3), half of them affected by an inherited autosomal-dominant monogenetic disorder which involves grammatical language impairment, orofacial dyspraxia and lower IQ. As the group showed, the affected members had a significant impairment in syntactic and grammatical test genetically mediated, but they did not know what gene was causing it.

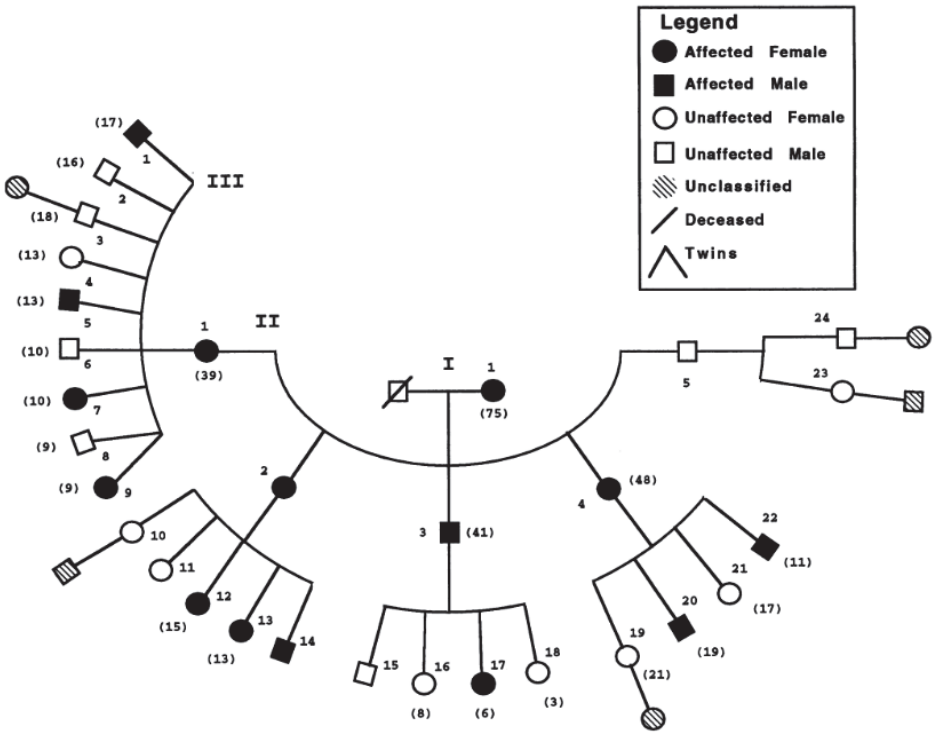

Figure 3 From Vargha-Khadem et al. (1995) KE Family pedigree showing the classification of affected and unaffected members. Roman numerals indicate the generation, and Arabic numerals outside parentheses indicate the member's pedigree number within a generation. (Numbers within parentheses indicate age attesting for those members who participated in the study.) Fourth generation members are infants and so have not yet been classified.

Fisher et al. (1998) following the description of their colleges of the KE family, were able to localize the possible gene in chromosome 7q31, calling this region SPCH1. Years later, Lai et al. confirm this finding in 2000 and were able, in 2001, to name the responsible gene for the disease and the mutation involved. They classified the gene into the forkhead/winged-helix (FOX) family of transcription factors due to the similarity of its DNA-binding domain; the mutation resulted to be an arginine-to-histidine substitution (R553H) at a highly conserved residue within the DNA-binding domain.

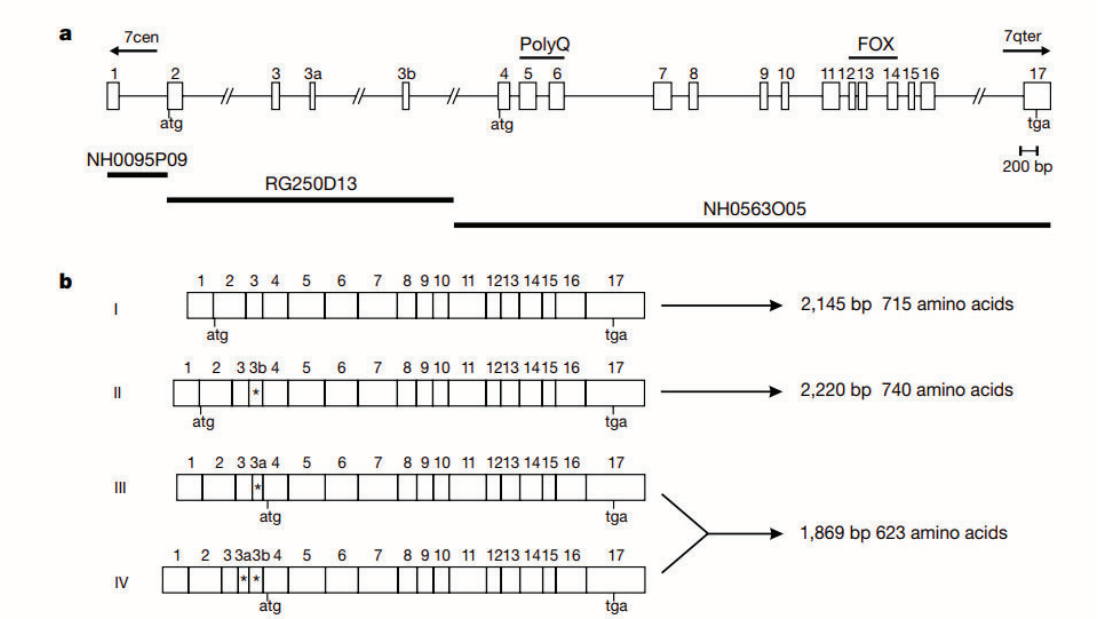

Figure 4 Lai et al. (2001) ***a)*** *Representation of human FOXP2 gene structure. Boxes represent exons, with positions of initiation and termination codons indicated. The scale shown applies only to exons; the entire region spans more than 267 kb of genomic DNA. Exons encoding polyglutamine tracts (PolyQ) and the forkhead domain (FOX) are indicated. The gene includes regions corresponding to expressed sequence tag ye50f03.r1 (exon 1), the partial CAGH44 transcript (exons 2±7) and a partial cDNA clone YX52E07 (exons 11±15). BAC genomic sequence entries are aligned beneath the gene structure.* ***b)*** *Alternative splicing of exons 3a and 3b (indicated by asterisks) leads to four different transcripts.*

Later investigation on the gene carried out by the same group (MacDermot et al. 2005) explored the possibility of other FoxP2 mutations related with speech impairment, and they were able to find another one: a heterozygous C→T transition in exon 7, creating a stop-codon at position 328 of the FOXP2 protein (R328X). These results ivied the gene with the title of the language gene, and it has been proposed to be screened in developmental verbal dyspraxia as a possible and likely cause.

The forkhead family

The first member of the family was described in 1989 and the transcription factor family was stablished after the description of HNF3 due to its resemblance to that of 1989. The family is composed by 19 subfamilies, going from FoxA to FoxS. The domain that gathered the different genes is the forkhead domain, build by three α-helices and three β-sheets surrounded by two loops forming the 'winged' region. The DNA binding occurs via the third α-helix and the major DNA groove and the second loop and the minor groove, as showed in Figure 5. Several studies have uncovered that the binding sequence of the FOX family can be asymmetrical the minimum consensus sequence has been proven to be 5'-(G/A)(T/C)(A/C)AA(C/T)A-3' (Carlsson et al., 2002).

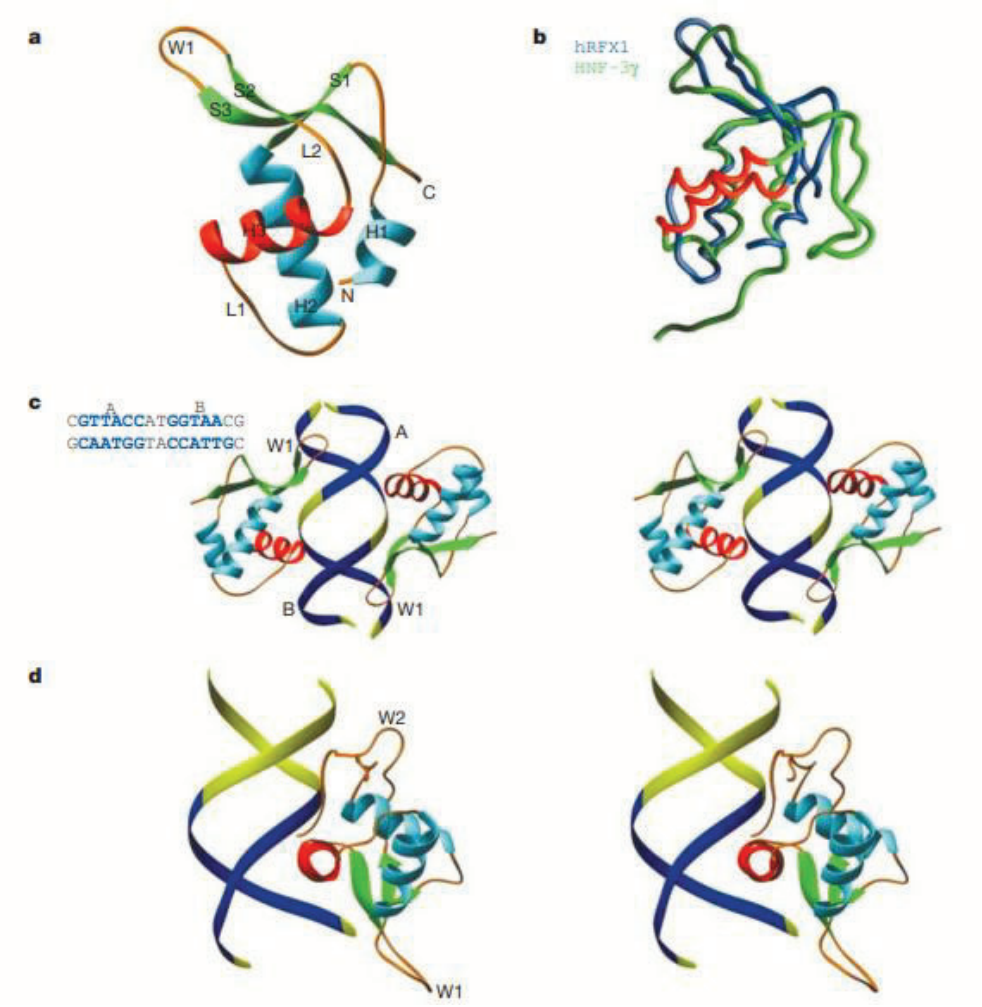

Figure 5 Gajiwala et al. (2000) Structure of hR

Members of this family work alone or by forming dimers, either with themselves, with other family members or with other transcription factors, depending on the tissue, the gene and the function carried out: activation or inactivation of genes (Herman et al. 2021).

FoxP2

The FoxP2 gene is the motor of differentiation in neurons, alveoli, and certain cell types in the gastrointestinal system (Shu et al., 2001). As shown above, the mutation R553H in the KE family is responsible of aberrational changes in neuroanatomy and orofacial structures which lead to the dyspraxia and language problems. But where is FoxP2 in the brain and how it works?

FoxP2 operates in neuronal cells by repressing genes related with progenitor-like state such as those involved in extracellular matrix organization or response to growth factors and by activating genes related neuron projection development or synapse structure, to name a few, both related with neuronal differentiation. Hickey et al. (2019) discovered that the region where FoxP2 actuates are predominantly enhancer regions, opening or closing the chromatin, what might exert their effects through long-range interactions with promoter regions. The mechanism by which this opening or closing of chromatin occurs varies depending on the FoxP2 cofactor involved: if it is DNA binding-dependent

closing, it requires a homodimerization of FoxP2; if it is DNA binding-independent closing, an heterodimerization occurs with another Forkhead motif, such as FoxP1 or FoxP4; the chromatin opening looks to happen due to an heterodimerization with HNI as a cofactor.

FoxP2, is key in neurodevelopment, as mentioned above, so here we want to sketch its implication in brain ontology and the temporospatial pattern of its unravelling. In the cerebral **cortex**, FoxP2 is highly enriched in layer 6 corticothalamic projection neurons and certain subpopulation of L5 pyramidal tract neuron. In the **hippocampal formation**, the paper played by FoxP2 is no clear and are FoxP1 and P4 the ones involved in its ontology. In the **amygdala** FoxP2 is expressed in the intercalated and anterior nuclei of the medial bed nucleus of the stria terminalis and in the basolateral and ventral nuclei of the lateral bed nucleus of the stria terminalis. This formation is implicated in controlling autonomic, neuroendocrine, and behavioural responses of the limbic system. In the **basal ganglia**, FoxP2 is expressed at high levels in direct spiny projection neurons and low levels in indirect spiny projection neurons of the striatum, lowly expressed in the globus pallidus, and coexpressed with FoxP1 in substantia nigra. In the **thalamus**, FOXP2 is expressed in sensorimotor nuclei. Finally, in the **cerebellum**, FoxP2 is expressed in the alar plate of the cerebellar primordium and later in the Purkinje Cells containing piriform layer of the cerebellum. Other regions where FoxP2 is expressed in ontology are medullary raphe, medulla oblongata, hypothalamus, and red nucleus. The role of FoxP transcription factors in the ontology of neural tissues follows a chronological organization, peaking in the prenatal period but it is postnatally maintained, in some degree, in certain not-fully-matured brain regions (Co et al. 2020).

FoxP2 network

FoxP2 operates as a transcription factor, as mentioned above, so it does not have any impact by its own in development and mediates via the genes which it regulates, some of which we are going to explain in the next lines (see Oswald et al., 2017 for more on this).

One of these regulated genes is moesin (MOE), implicated in the regulation of PTEN (Roubinet et al., 2011), a critical regulator of neuron development and survival, axonal regeneration, and synaptic plasticity (Ismail et al., 2012); and the ERM complex, involved in: cell–cell recognition, signalling, motility, regulation of neurite outgrowth and neuron motility (Antoine-Bertrand et al., 2011).

On hard tissue development, mainly in the orofacial region, two myosin genes are regulated by FoxP2: MYH8, related with retrognathia and prognathia disease (Oukhai et al., 2011); and MYH13, related with acquisition of adult larynx properties, conditioning the anatomical bases of speaking production (Périé et al., 2000).

FoxP2 also plays a role in microtubular dynamics via DCDC2, which directs neuronal migration by stabilizing microtubules and mutations of this protein has been related with communication impairments such as a form of deafness (Grati et al., 2015), variation of GMD in language-related brain regions of schizophrenia patients (Jamadar et al., 2011), reading disability (Meng et al., 2005) or dyslexia (Newbury et al., 2011); and

MARVELD1, a negative regulator of PIK3K/AKT-mediated myelination in central and peripheral nervous system (Noseda et al., 2016).

FoxP2 cascades by regulating other transcription factors such as: NURR1, related with dopaminergic function (Kim et al., 2015); PHOX2B, regulator of the differentiation of hindbrain visceral and branchial motor neurons (Hirsch et al., 2013); SEBOX, involved in postnatal brain maturation (Cinquanta et al., 2000); and FoxL1, related with midbrain development (Nakada et al., 2006). It is also involved in JAK/STAT cascade, related with the pathogenesis of Down syndrome (Lee et al., 2016), neuro-inflammatory diseases via interleukin modulation (Seki et al., 2002), and dopaminergic neurodegeneration (Qin et al., 2016); and STAT3, STAT5B, and STAT6; modulators of neuron survival (Tyzack et al., 2014), synaptic plasticity (Deboy et al., 2006), and neurite outgrowth (Georganta et al., 2013).

Gene silencing is performed via TARBP2, DICER1, and EIF2C1-4, all of them regulated by FoxP2, also stablishing a negative feedback loop silencing FoxP2 itself. Interestingly, EIF2C1 and EIF2C3 have been related with facial dysmorphologies, speech and motor delay, and moderate intellectual disability (Tokita et al., 2015), while DICER1 and EIF2C2 have been related with Huntington disease (Banez-Coronel et al., 2012), another dopamine related condition.

Objectives

Main objective:

Our main goal with this systematic review is to cast some light on the implications of the different SNPs of FoxP2 in relation with some aspects of schizophrenia: as a risk factor, as an illness modulator or as a treatment disruptor or enhancer. Given its central function as an ontological gene in brain development, our hypothesis is that its alteration can modify how SCZ manifests, and our aim is to picture the current scientific knowledge in this regard to be able to chart what is left unknown and guide future research.

Secondary objectives:

In our aim to chart the implications presented above, we expect to be able to (1) explore the relationship of FoxP2 with other cognitive domains in SCZ, (2) combine the neuroimaging findings with the neurological network of SCZ, (3) extend the relationships of FoxP2 with other mental illnesses, (4) look into the potential differences based on environmental factors such as ethnicity or trauma exposition, and (5) evaluate the potential differences based on personal factors such as metabolic scores or sex.

Methods

This work has been conducted following PRISMA criteria for systematic reviews (Page et al., 2021). First, we conduct a search in two different databases, PubMed and EMBASE, using the words “FoxP2” AND “schizophrenia”. All found articles until end of April 2023 have been considered for inclusion in our systematic review. More bibliographical references have been explored in the reference lists of other articles, but no additional results were found by this way.

Second, we established the inclusion and exclusion criteria for studies to be considered in our review. The inclusion criteria were:

- Studies based in humans.
- Written in English or Spanish
- Studies that explored already codified SNPs of FoxP2 gene
- Studies that investigate a direct relationship between FoxP2 and SCZ

The exclusion criteria were:

- Reviews, meta-analysis, case-reports, editorial letters, posters, and conference abstracts
- Animal models
- Written in other languages different to English or Spanish
- No direct relationship between FoxP2 and SCZ is explored in study´s results

If the inclusion of each work were not clear after reading tittle and abstract, the entire study had to be analysed. When after this, remains unclear, inclusion was discussed with director of this work.

To systematise the information included in all articles, an Excel database was performed containing the following information of each article:

- General data: tittle, authors, year, country
- Descriptive information: sample size (n), median age of participants, gender, mental disorder, length of illness.
- Genetic information: type of SNP,
- Schizophrenia risk association YES/NO, and ratio of risk (Odd ratio, relative risk, etc) if any.
- Type of association (if any): clinical symptomatology, illness risk, cognitive scores, language scores.
- Neuroimaging and brain structural changes related to FoxP2 expression.
- Results and conclusions.

For heuristic reasons, articles were classified according to the main outcome, in different groups: 1) Studies focusing on genetic variation in the FoxP2 gene and its potential relationship to schizophrenia, 2) Studies exploring the expression and grey matter density of FoxP2 in the brains of patients with schizophrenia; 3) Studies investigating the association between FoxP2 and cognitive deficits or language impairment in schizophrenia; and lastly, 4) Studies exploring potential interactions between FoxP2 and other factors, such as childhood emotional abuse or Body Mass Index (BMI).

This systematic review has been registered in PROSPERO.

Results

Description of the included studies

Figure 6 shows the flow-chart of our search.

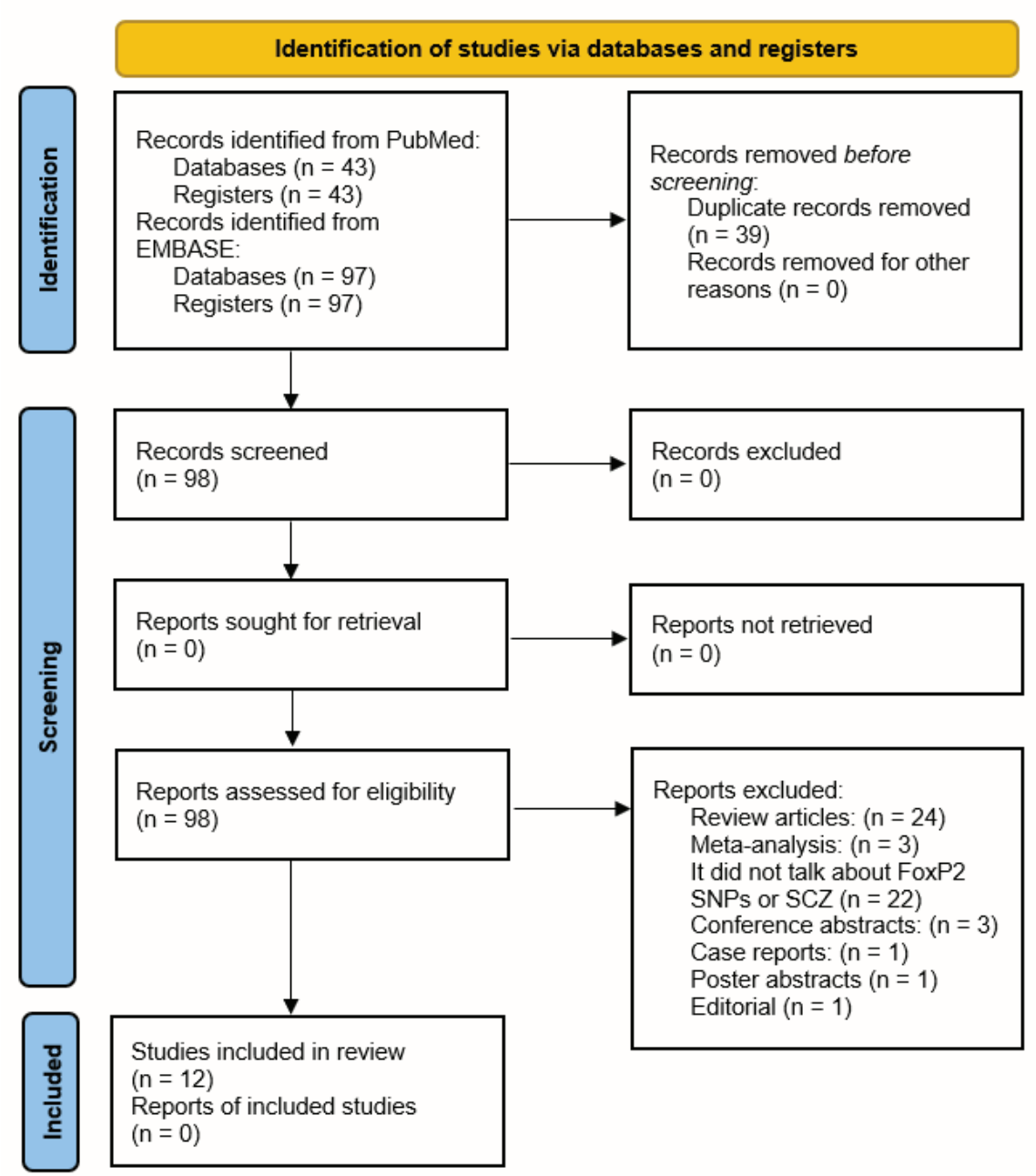

Figure 6. PRISMA Flow-chart (Page et al., 2021)

Overall, we obtain 138 results, 97 in EMBASE (Figure 7) and 41 in PubMed (Figure 8). We eliminated 39 repeated studies, and we applied the inclusion and exclusion criteria to a total of 98 studies. Out of them, 28 studies were not related studies, 24 were review articles, 22 studies did not research any FoxP2 SNP, 3 were meta-analyses, 3 were conference abstracts, 1 was a case report, 1 was a poster abstract and 1 editorial. We ended up with 12 studies to review, with a total number of 50 analysed SNPs.

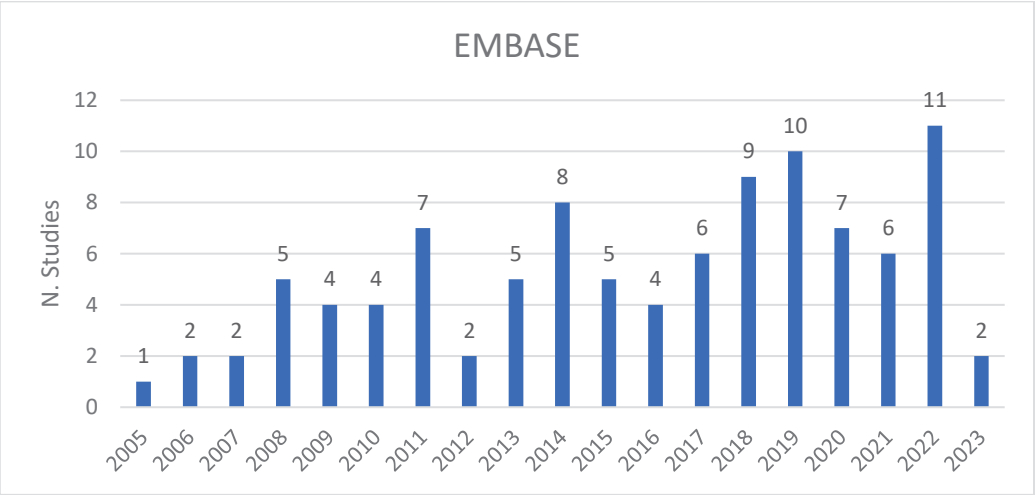

Figure 7. Publication years in EMBASE

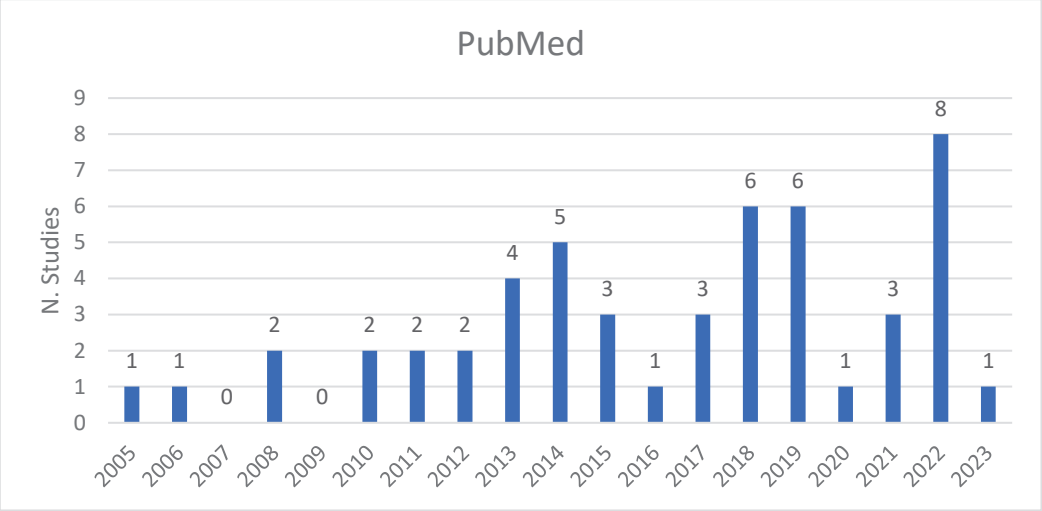

Figure 8. Publication years in PUBMED

The majority of the studies were conducted in Eastern countries, specifically China and Australia, with a few studies from the United States, the United Kingdom, and Spain. The publication years ranged from 2005 to 2023, with the highest number of publications in 2019 and 2022 (see Figures 2 and 3). The sample sizes varied widely, ranging from 24 to over 2,000 participants.

Related to the main outcome, some studies focused on genetic variation in the FoxP2 gene and its potential relationship to schizophrenia risk (N=4), while others explored the expression and grey matter density of FoxP2 in the brains of patients with schizophrenia (N=2). Several studies investigated the association between FoxP2 and cognitive deficits or language impairment in schizophrenia (N=9). A few studies (N=2) explored potential interactions between FoxP2 and other factors, such as childhood emotional abuse or BMI. It is worth noting that any of included articles studied the relationship between FoxP2 gene the response to psychopharmacological treatment.

Table 1 summarize the included articles.

FoxP2 and Risk of schizophrenia

Four studies contemplated the relationship between several FoxP2 polymorphisms and schizophrenia risk. Below, the reader has a summarised version of each study focusing on this associations and some of the limitations encountered. The total number of SCZ patients was 2623 and the total of healthy controls was 1684.

Sanjuán et al. (2005) looked for an association between the risk of developing SCZ and the SNPs rs936145 and intron3a, finding no association whatsoever in a sample of 138 SCZ, 11 schizoaffective patients and 137 healthy controls. It is worth noting that the patient sample consisted in psychotic patients with active auditory hallucinations, including acute SCZ and schizoaffective patients, but not properly stabilized SCZ patients.

Rao et al. (2017) studied if FoxP2 rs10447760 was related with the risk of developing SCZ in Han Chinese population by comparing 1069 SCZ patients with 410 healthy controls in a case-control study. They did not find any significant difference in allele distribution between patients and controls.

Yin et al. (2018) performed an association analysis of rs10447760 in a case-control study with 1405 SCZ patients and 1137 healthy volunteers in Han population, concluding that this SNP might not be a risk locus for susceptibility to SCZ. Because there is some controversy around this particular SNP, they discussed in the possible limitations of their study that their results may be due to an ethnic-geographical aspect.

Finally, Lang et al. (2019) while studying the relation of FoxP2 SNP rs10447760 in chronic SCZ patients and healthy controls regarding cognitive function, observed that indeed, rs10447760 may not be related with the risk of developing SCZ.

Therefore, our review shows that SNPs Intron3a, rs936145, rs10447760 seem not to be associated with SCZ risk in the four included articles which contemplated this aspect. However, two of these studies were conducted with Han Chinese population, and the other one with Spanish population.

FoxP2 as modulator of clinical and cognitive function in SCZ

Three studies explored any relationship betweenFoxP2 gene as modulator of SCZ psychopathology. The total sample size is compounded of 867 SCZ and 402 HC

The group of Sanjuán (2005) also looked for an association between SNPs rs936145 and intron3a and clinical symptomatology, measured by the PSYRATS (Psychotic Symptom Rating Scale) and Krawiecka scale, focusing on auditory hallucinations and formal thought disorder (*incoherence*), respectively. The study showed negative or no significant results. However, authors mentioned some of the limitations of these findings, since the patients were no assessed for cognitive or language impairments and all included patients had active auditory hallucinations, so they could not test correctly for this association in particular.

In Rao et al. (2017) study, they also compared the FoxP2 SNP rs10447760 with clinical symptomatology of SCZ, defined by the PANSS (Positive and Negative Symptoms Scale), and in this case they did find a significant difference in PANSS total score, positive

symptomatology score and general psychopathological scores between SCZ. Specifically, patients with the CC genotype had higher symptomatologic and psychopathological scores than those with the CT genotype, however, PANSS total did not survived Bonferroni correction, but remained statistical signification in symptomatology and psychopathology scores and these differences persisted after correction for treatment duration, BMI, gender, age, education, illness course and age of onset. Authors discussed later that their results could be misleading due to low sample size. They also remarked that the chosen patients had severe psychopathology and longer illness duration than the typical psychotic treatment-naïve patients.

Lang et al. (2019) studied the implications of FoxP2 SNP rs10447760 in chronic SCZ patients and their cognitive impairment evaluated by the RBANS (Repeatable Battery for the Assessment of Neuropsychological Status). In a sample of 867 SCZ patients and 402 healthy controls they found that rs10447760 is related with a decrease in every aspect of the RBANS except for the visuospatial/constructional score, which remained like that of healthy controls. The most affected score was immediate memory, with a remarkable decrease in the CT genotype group in comparison with that of the CC group. It is worth noting that the TT genotype was not present in the sample. They also highlighted that it may be confusing to evaluate cognitive impairment in chronic SCZ patients, because of different antipsychotic medications and length of illness. Besides, they remarked the limitations of evaluating cognitive function by RBANS, that only measured five cognitive domains, due to the complexity of general cognitive function.

To summarise, two of three included studies showed a relationship between FoxP2 gene and some aspects of the clinical psychopathology of SCZ. Specifically, allele C of rs10447760 was founded to be related to psychopathology and clinical symptoms of schizophrenia, and to immediate memory in SCZ patients. Moreover, the study that could not show a relationship between FoxP2 and clinical aspects of SCZ was focused on different FoxP2 polymorphisms (rs936145 and intron3a).

Fox P2 as modulator of language in SCZ

Six studies explore the relationship between language, as a clinical characteristic of SCZ, and FoxP2 polymorphisms. The total sample included in those articles was 2757 SCZ patients and 1802 healthy controls.

Sanjuán et al. (2006) explored the association between auditory hallucinations measured by the Manchester scale and those measured by PSYRATS in a sample of 186 SCZ patients and 160 healthy controls. Forteen FoxP2 SNPs were evaluated: rs6466478, rs7803667, rs10447760, rs7784307, rs10276237, rs7798050, rs923875, rs1597548, rs2396722, rs1358278, rs1852469, rs2396753, rs17137124 and rs1456031. Of all fourteen SNPs, only rs2396753 was significantly related with auditory hallucinations after Bonferroni correction. They also found an association between rs2396722 and rs1358278 and incoherence of speech, but it failed to reach significance after Bonferroni correction. With rs7803667 and rs10447760 it looked like there was an association with frequency, duration and disruption of life of the auditory hallucinations in SCZ patients, but it did not pass Bonferroni correction. In particular with rs10447760, it seemed to be also associated with the amount of content and the amount and intensity of distress of the auditory hallucinations, but the again was not significant after Bonferroni correction.

In addition, the following combination of alleles rs7803667T/rs10447760C/rs923875A/ rs1358278A/rs2396753A and rs7803667A/rs10447760T/ rs923875C/rs1358278G/ rs2396753C seemed to be related with auditory hallucinations in patients with SCZ, being the first haplotype considered as a risk factor for hallucinations and the second a protective one.

Tolosa et al. (2010) investigated the possible association between twenty-seven FoxP2 SNPs and poverty of speech or the intensity of auditory hallucinations in a sample of 293 SZC patients and 340 controls. In their study, they also performed the possible implications of trinucleotide expansions and the methylation of CpG island in post-mortem brain samples, although analysing these is not the aim of our review. It seemed that SNP rs2396753 and SNP rs17137124 were associated with auditory hallucinations, but the association did not prevail after Bonferroni correction. The only association that remained significant was that of rs2253478 and poverty of speech. They also carried out an haplotypic association analysis finding that haplotype rs7803667T/rs10447760C/ rs923875A/rs2396722C/rs2396753A, the same combination found by Sanjuan et al. (2006) to be protective against auditory hallucinations.

McCarthy-Jones et al. (2013) explored the relation between parental child abuse and the risk of developing auditory verbal hallucinations (AVH) in a sample of 333 patients diagnosed by any psychotic disorder (211 patients had a history of AVH and 122 did not.). They also confronted their results with some FoxP2 SNPs: rs1456031, rs2253478 and rs2396753. The type of AVH explored were those defined by the DIP (Diagnostic Interview for Psychosis) in the 51, 52 and 53 item (I.e., accusatory/abusive/persecutory/commanding voices; running commentary voices; and third person voices). They found a positive association between AVH and childhood trauma in those patients carrying C allele of rs1456031. Authors also concluded that experiencing AVH was a risk factor for developing auditory non-verbal hallucinations too, and that the negative symptoms were more common in the AVH group. Regarding FoxP2, rs1456031, seemed to be related with experiencing AVH but in a different direction depending on the genotype and the history of parental emotional child abuse (Figure 9): the CC genotype acts as a risk factor for AVH if there is parental emotional abuse, but it acts as a protection factor if the parental emotional child abuse is absent; the opposite is true for the TT genotype acts as a risk factor if there is no parental emotional child abuse and as protection factor with parental emotional child abuse. The authors also tried to find any association between FoxP2 SNPs and AVH without considering the parental child abuse, but no association was observed. They remarked the limitations of their investigation: first, the sample size was not large enough to firmly confirm their results; second, they focused on parental child abuse without exploring the possible associations with other modalities of trauma; third, they did not investigate other possible non-genetic factors for AVH such as self-blame or isolation or anger. They also mentioned some possible paths to explore, such as the relationship between FoxP2, verbal fluency and AVH, the environmental regulation of FoxP2 or the implications of FoxP2 in the activation of the frontotemporal network responsible for the AVH.

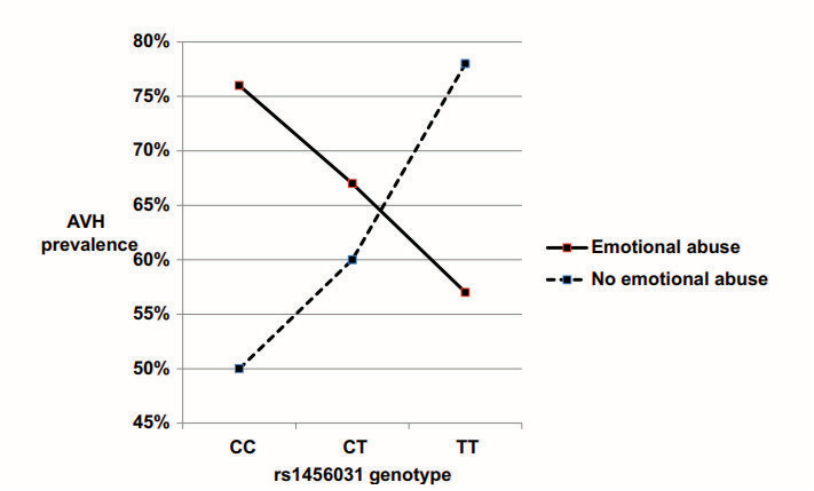

Figure 9 From McCarthy-Jones et al. (2013). Relationship between FoxP2 rs1456031 and AVH depending on the presence of parental emotional child abuse in SCZ patients.

In Lang et al. (2019) study, mentioned above, revealed a language impairment in RBANS scores depending on the genotype of rs10447760, showing that SCZ patients had lower scores (74.77±18.11) than healthy controls (94.02±13.03) for the CC genotype, and 71.94±18.10 in CT genotype SCZ patients versus 86.00±17.94 in CT genotype controls. It is worth noting the difference in sample between SCZ patients and controls with the CT genotype, 31 SCZ patients versus 5 controls, so as they mentioned, small changes in the results for the CT genotype could change the significance dramatically. Also, the TT genotype was absent in the sample, so it remained unexplored.

The group of McCarthy et at. (2019) tried to find a relationship between 5 previously language-related FoxP2 polymorphisms (rs2253478, rs2396753, rs7799109, rs17137124, rs1456031) and language impairment in SCZ, measured by the FAS version of the COWAT (Controlled Oral Word Association Task) test, SPQ (Schizotypal Personality Questionnaire) and the DIP (Diagnostic Interview for Psychoses). The sample consisted of 333 SCZ patients, 232 unaffected first-degree family members of them and 144 healthy controls, all of them from the WAFSS (Western Australian Family Study of Schizophrenia). They did not find any significant relationship in their study, arguably because they tested 5 different SNPs with 5 different language measurements (25 tests in total for a sample of 709 people) making the total error unbearable.

Recently, (17) Yang et al. (2022), in a sample of 867 SCZ patients and 402 controls, explored the implication of sexual dimorphism in the relationships between FoxP2 rs10447760 and BMI regarding the cognitive deficits in SCZ. Their results showed that male patients with SCZ had better language scores than those of female patients; in this effect, rs10447760 had some influence: in male SCZ patients, the CC genotype positively linked BMI and language scores. However, no association between rs10447760 and language scores alone was found. They neither found an interaction between rs10447760 and sex on cognitive performance. Some limitations must be remarked here: they did not used similar sample size nor between patients and control, neither between males nor females. As happened in previously summarized studies, the rare T variant of rs10447760 make the results somewhat doubtful, changes in the CT group size could change the results radically.

Briefing, the most studied SNP of FoxP2 in relation with language has been rs10447760, discovering that: the CC genotype seemed to be associated with lower language scores than those of the CT genotype (Lang et al. 2019) but recent studies showed that it was not associated (Yang et al. 2022); sex is not a modifying factor of its function in relation with language alone, but if BMI is also taken into account, the CC genotype is positively associated with BMI in male SCZ patients (Yang et al. 2022). It is worth noting that the T allele of this SNP is rare, so small changes in the CT or TT group could change the results wildly. On rs1456031, parental child abuse could act differently, depending on the allele, in the development of AVH: the C allele seems to be a risk factor and the T allele a protective factor. However, the opposite happens if the parental child abuse is absent (McCarthy-Jones et al. 2013). Other explored SNPs have not shown any relationship with language (Sanjuán et al. 2005) but this can be due to the relatively small sample size.

FoxP2 and neuroimaging changes in SCZ

Only two studies investigated the relationship of FoxP2 SNPs with neuroimaging changes related in SCZ.

Spaniel et al. (2011) compared the MR images from genotyped SCZ patients with those from healthy controls in looking for an association between FoxP2 rs2396753 and grey matter density (GMD). They found that SCZ patients had lower GMD than healthy controls, especially in prefrontal and temporal areas, and also in amygdalar, bilateral insular, anterior cingulate, bilateral premotoral, right somatosensorial and bilateral superolaterotemporal areas. Other regions showed similar GMD reductions such as bilateral cerebellum, right basal ganglia, bilateral parietal and left occipital lobes. They did not find any area with higher GMD in SCZ patients. Reductions in the GMD were classified depending on the rs2396753 haplotype, showing that SCZ AC patients had lower GMD than any other group (note that there were only one SCZ CC patient, and for that reason was excluded from comparison). It is worth noting that there were no significant differences in GMD between SCZ AA group and healthy controls AA group.

Sanjuán et al. (2020) studied the SNP rs2396753 and its association with GMD in male patients. They compared the FoxP2 expression in the prefrontal cortex (PFC) in samples from 61 genotyped SCZ patients and 18 healthy controls with the neuroimages from 48 genotyped SCZ patients and 36 healthy controls to prove the association between FoxP2 haplotypes and lower GMD. They found that FoxP2 expression was reduced in the PFC of SCZ patients. The AA group had higher expression than the AC or the CC group. Another discovery was that SCZ patients had lower GMD in insular, temporal, frontal and cingulate areas. The CC SCZ subjects showed significant decrease in comparison with the AC or the AA SCZ subjects. The AC patients had lower GMD than the AC controls. One of the things the authors remarked is the difference in sample size of SCZ patients was bigger than that of controls in regard with the AA and the CC genotypes, which made incomparable the effect of those genotypes in GMD. Those results should be interpreted with caution as alleles of rs2386753 were not in Hardy-Weinberg equilibrium (HWE) for the SCZ patients.

Both studies explored the same SNP, rs2396743, casting approximately the same results: in patients with schizophrenia GMD is lower if the C allele is present. The affected regions by this effect in both studies are nearly superposed.

FoxP2 and other mental illnesses

Li et al. (2013) studied the effects of 12 different FoxP2 SNPs with different identical-size (1135) samples of SZC patients, major depression (DEP) patients, bipolar disorder (BD) patients and healthy controls. Only rs10447760 was related with SCZ and DEP. Besides, a previous SNP historically related with SCZ, rs2396753 (Sanjuán et al., (2006) (see above)), showed to not be associated with SCZ in Han Chinese patients. As happen in previous investigations, small changes in numbers of rare SNP groups could dramatically alter the significance of the results.

Discussion

Summary

We have review 12 different studies focused on FoxP2 polymorphisms and different aspects of SCZ: risk of development, clinical psychopathology, cognitive and language-related symptoms, neuroimage and overlapping with other psychiatric disorders. Our research found that no studied FoxP2 polymorphism seem to be related with SCZ risk, despite the efforts of the scientific community and the number of SNPs tested (N=50). FoxP2 rs10447760 has been studied several times and it may be involved in the manifestation of SCZ as a clinical entity, increasing the psychopathological scores in patients affected by this SNP. Besides, its expression is related with other clinical data such as sex or BMI. However, the rarity of its T allele in analysed studies make us take these results with a pinch of salt. On the other hand, auditory verbal hallucinations and rs1456031 is a relationship worth remarking because it opens the analysis of FoxP2 SNPs and environmental and biographical factors in the outburst of SCZ. The only relationship we have found between FoxP2 and language in SCZ is that of rs2253478 and poverty of speech. Finally, regarding image studies, FoxP2 rs2396753C shows to be one of the key factors in the decrease of GMD in SCZ patients, one of the anatomical landmarks of the disease.

First of all, we think is important to describe and locate more precisely each relevant SNP in the FoxP2 gene to orient the reader for what is coming.

- SNP **rs10447760** is located in position 114083210. The C allele frequency of 78% and 22% that of the T allele globally. It is worth noting that it is a non-coding SNP, just as happens with the other studied SNPs. (rs10447760 RefSNP Report - dbSNP - NCBI (nih.gov))
- SNP **rs1465031** is located in position 114656047 and its allele frequency is 54% for the T allele and 46% for the C allele. (rs1465031 RefSNP Report - dbSNP - NCBI (nih.gov))
- SNP **rs2253478** is located in position 114337941 and its allele frequency is 41.5% for the A allele and 58.5% for the G allele. (rs2253478 RefSNP Report - dbSNP - NCBI (nih.gov))
- SNP **rs2396753** is located in position 114508276. The A allele frequency is 60% and 40% for the C allele, but there is a very rare G allele. (rs2396753 RefSNP Report - dbSNP - NCBI (nih.gov))

Demonstrated FoxP2 influence:

There is a substantial body of research regarding the "language gene" and its pathological influence in psychiatric and no psychiatric diseases, due to its transcription factor function and the multiplicity of genes that it regulates (see Introduction). Here we present some of that body of research depending on the disease investigated:

After the Lai et al. (2001) definition of FoxP2 as a language gene by the KE family (see above), Kay et al. (2005) demonstrated that R328X nonsense mutation of FoxP2 gene is a direct aetiological cause alone for verbal dyspraxia, invoking the possible need for a FoxP2 screening in dyspraxia patients, given the ∼6.1% frequency of mutations in the FoxP2 protein. Recently, following the same line, Turner et al. (2013) reported the consequences of an intragenic deletion of FoxP2 located before the DNA-binding domain in a male child patient, causing him a severe motor speech disorder, impaired word reading, spelling and phonological awareness skills, as shown in the KE family. There are other studies in this field of research, such as Rice et al. (2012) or Zeesman et al. (2006).

As we introduced above, the FoxP family is expressed in the lungs and gastrointestinal tube, as Shu et al. (2007) showed in their study, FoxP2 is crucial in alveolarization by repressing T1alpha gene expression and in oesophageal muscle development influencing muscle cell differentiation.

In relation to the central nervous system (CNS), Premi et al. (2012) found an association between FoxP2 rs1256031 and rs17137124 with PPA (Primary Progressive Aphasia), causing worse perfusion in the left inferior/middle frontal and superior temporal cortices depending on the number of copies of the T alleles, with greater effect if both SNPs are present. Park et al. (2018), studying the relationship between FoxP2 and MAOA polymorphism found that the interaction of both *FOXP2*-TCGC (rs12531289-rs1350135-rs10230087-rs2061183) diplotype and *MAOA*-TCG (rs6323-rs1801291-rs3027407) haplotype is related with autism spectrum disorder (ASD) and language scores in male patients. Rodríguez-Urgellés et al. (2022) found a decrease of FoxP2 in striatal neurons of R6/1 mouse model for Huntinton Disease causing impulsivity, hyperactivity, and social disturbance and, interestingly, recovering from impulsivity and aggressivity behaviour after lateral intrastriatal injections of a FoxP2 viral vector.

A 2017 study by Crespi et al. found that, in fact SNPs rs1456031, and also rs7799109, are associated with one or more inner speech or speech fluency phenotypes, however, they were healthy population. Still, this is in line with McCarthy-Jones et al. (2013) and their study of AVH and FoxP2 SNPs, given the relationship between inner speech and AVH (Upthegrove et al., 2015).

Despite our SNPs are located in noncoding regions of FoxP2, a body of research exists regarding how the **noncoding genome** is involved in gene 3D structure and expression. Orozco et al. (2022) reviewed this spatial organization of the genome and how influences the cellular genetic fate via interaction with regulatory element such as enhancer or silencers, remarking the impact of non-coding SNPs in this regard. Furthermore, the non-coding DNA of highly conserved developmental genes, such as FoxP2, is fundamental for its chronotopical activation in ontology (Woolfe et al., 2004).

Regarding the influence of FoxP2 in **neuroanatomy**, there are several studies which demonstrate how some SNPs are related with certain psychiatric and neurological based diseases. We have already mentioned some of them (Premi et al., 2012; Rodríguez-Urgellés et al., 2022) and how FoxP2 is related with neurodevelopment (see Introduction).

If we focus our research in **how the environment regulates gene expression**, some studies cover the implications of certain environmental factors in FoxP2 expression, as has been suggested by McCarthy-Jones et al. (2013) and their study of AVH or by Yang et al. (2022) and their study of BMI. In this regard, the relationship between BMI and cognitive performances has already been explored by different groups, casting results similar as those declared by Yang et al. (2022). In a 2016 study, Marioni et al. found an overlap between both biological pathways, remarking genes as those related with insulin processes (AKAP6), lipid transportation and Alzheimer's disease (TOMM40), retinal arteriolar calibre (TMEM161B) and height (TNRC6B).

Non demonstrated FoxP2 influence:

We have talked about the study of Park et al. (2018) and ASD but is worth noting how the association found was only preserved if both the FOXP2-TCGC and MAOA-TCG were present, pointing at the possible interactions yet to be covered to draw the complexity of FoxP2 in disease. To exacerbate those findings, a study of 2021 conducted by Yalçintepe et al. Found no relationship between SNPs of FoxP2 and ASD, going against previous results.

The relationship casted by McCarthy-Jones et al. (2013) between FoxP2, AVH and parental child abuse, even with its precision, lacks in explanation: despite the relationship between FoxP2 and the hypothalamus or the pituitary gland are still not explored properly, neither the influence of stress of FoxP2 expression, there are studies which explore the relationship between the stress caused by child abuse and hypothalamic-pituitary-adrenal (HPA) axis response (Kuhlman et al., 2018), and it is demonstrated the relationship between high HPA axis baseline activity and SCZ (Walker et al., 2008). However, no significant interaction between stress and FoxP2 expression has been studied, so this remains a line for future investigation.

It is remarkable the lack of studies between FoxP2 and PTSD (Post-traumatic stress disorder), what may be a rich vein to explore in future papers, due to the relationship that exist between PTSD, trauma and the HPA axis (Dunlop et al., 2019) and between PTSD and language (Todorov et al., 2020).

There is a more recent study regarding the effect of FoxP2 polymorphism and neuroanatomy (Hoogman et al., 2014) with results opposite to those found by Spaniel et al. (2011). In their study they analysed 9 SNPs of 1301 healthy participants, and no significant association was found with any of the SNPs analysed. They remark thought that previous studies investigated the effect in disease cohorts, such as SCZ, so the effect may be mediated by other involved genes.

Psychosis is a broad term that involves a *loss of reality* defined by delusions, hallucinations and thought disorder (Gaebel and Zielasek, 2015). There is evidence that

trauma can alter the attributional style, leading to an aberrant perception of oneself, the others and the world (Kilcommons et al., 2005), conveying the subject to a state pre-psychotic perception. How FoxP2 influences this perception may be relevant in understanding the etiopathology of psychosis. In this regard however, a study of 2015 by Mueller et al. showed that common coding variants of FoxP2 are not related with language scores in children, a relevant finding due to the relationship between language, attributional style and hallucinations (Upthegrove et al., 2016).

Limitations

The main limitation of our study is the reduced number of studies in this field (N=12). Despite our effort to select as many articles as possible by being more permissive with the exclusion criteria and broadening our search in another database, we could not find more about our topic, regardless of its now uncovered potentiality.

One of the most obvious limitations we have encountered is the male/female ratio of the literature analysed. It is remarkable because the incidence of SCZ is not very different between sexes, although some studies (McGrath et al., 2008) have shown a ratio of 1,4:1, while ours is 1,7:1. It is remarkable how some studies not even describe sex differences in their methods, as can be seen in Table 1.

The mean sample size of our review was 773 patients and 350 controls, but every analysed study remarked in its discussion that small changes in allelic groups could change the results wildly, due to the scarcity of some variants, as happens with rs10447760T, for example.

Following the sample limitation, the subgroup analyses of the samples would lead to a higher error rate in an already precarious sample size. This meant that some of the possible comparisons, such as sex, age or treatment length, has been left aside until new research cover them.

Mental disorder symptomatology falls in a rather difficult to measure category. In a 2011 paper Obermeier et al. revealed how PANSS has been used incorrectly in more than 60% of published articles of high impact journals. They point to a Percent Changes Scores rather than a punctuation score to measure symptomatology improvements.

None of the analysed studies deepen in why non-coding SNPs may have an impact in the variables analysed. As it is said above (Orozco et al., 2022), the 3D structure of the genome is influenced by this non-coding DNA, and to this point, no study has cast any light in how the SNPs mentioned in our review modify the promoter-enhancer tandem in FoxP2.

As mentioned in the introduction, the ontological pathways in which FoxP2 acts has been somewhat stablished and some of the proteins mentioned above could have been measured to broaden and explain some of the conclusion some authors have come.

Finally, an inherent limitation of our review, as usually happens in systematic reviews and meta-analysis (Dalton et al., 2016), is the publication bias, the tendency to publish “only results that are statistically or clinically significant” so, again, our casted results should be taken with care.

Contributions

At this point, we think is important to chart the unexplored paths in the relationship between FoxP2 and SCZ, so we can take a clear picture for the future investigations and possible lines of research in relation to our review.

First, although FoxP2 has been studied as a possible **risk factor** of SCZ, there still are a significant number of SNPs not yet studied, and even those that has been studied, the sample size may have not been sufficient. This last conclusion can be extended to the rest of remarks.

Second, the evolution of **first episodes** of psychosis has not been evaluated depending on the SNP present, so we do not know yet if there are SNPs related with better or poorer outcome depending on the age, sex, causes and circumstances that trigger a psychotic crisis and if FoxP2 is behind its unravelling.

Third, some **positive and cognitive symptoms** of the disease have been studied regarding FoxP2 polymorphisms but, as we have covered at the introduction, SCZ symptomatology is vast and complex, and the scientific community has only covered a few aspects of its manifestations (i.e. AVH, the cognitive spectrum measured by RBANS or the PANSS score) depending on the SNP present, leaving the rest unexplored.

Forth, here we have talk about parental child abuse as an **extrinsic factor** influencing the manifestation of SCZ depending on the FoxP2 SNP present, but as we have presented in the introduction, there are more external environmental factors, prenatal, childhood or early adulthood that has not been investigated yet.

Fifth, nothing has been investigated related with **treatment response** concerning FoxP2 SNP, and it has not been taken into account the difference in treatments and treatment duration in the evaluation of some of the symptoms explored. This leaves the door open for further investigation in how the language gene influence treatment and illness progression depending on the drugs used.

Conclusions

We have analysed 12 studies that try to relate FoxP2 SNPs with SCZ. Of all 50 SNPs analysed in total, only rs10447760, rs1465031 and rs2396753 have shown to be significantly related with some aspects of the diseases: rs10447760 is related with some clinical manifestation of the disease measured by RBANS and PANSS, and with BMI in SCZ patients; rs1465031 is related with AVH and parental child abuse; and rs2396753 is related with GMD reduction in SCZ patients. The main limitations of the studies analysed was the small sample size, making some of the results modestly unreliable. There is still a great amount of SCZ aspects not explored in relation with FoxP2, so the final picture has not been taken yet.

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Acknowledges

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ANNEXES:

TITLE	AUTHORS	YEAR	COUNTRY	PATIENT SAMPLE SIZE	CONTROL SAMPLE SIZE	SNPs
FOXP2 polymorphisms in patients with schizophrenia	Sanjuan et al.	2004	Spain	149 P (107m/42f) - 138 SZC - 11 SCZ-AFF	137 HC	Intron3a rs923875 R533H
Association between FOXP2 polymorphisms and schizophrenia with auditory hallucinations	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
FOXP2 gene and language impairment in schizophrenia: association and epigenetic studies	Tolosa et al.	2010	Spain	293m SCZ	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

Genetic variation in FOXP2 alters grey matter concentrations in schizophrenia patients	Spaniel et al.	2010	Czech Republic	40 (18m /21f) SCZ	36 (17m/19f) HC	rs2396753
FoxP2 is significantly associated with schizophrenia and major depression in the Chinese Han population	Li et al.	2013	China	3405 P: - 1135 SCZ (630m/505f) - 1135 DEP (483m/652f) - 1135 BD (618m/517f)	1135 HC (369m/766f)	rs6466488 rs1025010 rs1563408 rs6960610 rs9969232 rs2189015 rs1456029 rs17137124 rs923875 rs1358278 rs2396753 rs10447760
Preliminary evidence of an interaction between the FOXP2 gene and childhood emotional abuse predicting likelihood of auditory verbal hallucinations in schizophrenia	McCarthy-Jones et al.	2013	Australia	333 (217m/116f) P: - 251 SCZ - 42 SCZ-AFF - 34 NOS (Not Otherwise Specified) - 6 DD (delusional disorder)	No control group	rs2253478 rs1456031 rs2396753
Association between forkhead-box P2 gene polymorphism and clinical symptoms in chronic schizophrenia in a Chinese population	Rao et al.	2017	China	1069 (778m/204f) SCZ	410 (163m/244f) HC	rs10447760
No association between FOXP2 rs10447760 and	Yin et al.	2019	China	1405 (875m/530f) SCZ	1137 HC (630m/ 507f)	rs10447760

schizophrenia in a replication study of the Chinese Han population						
No association between common genetic variation in FOXP2 and language impairment in schizophrenia	McCarthy et at.	2019	Australia	333 (261m/72f) SCZ/spectrum disorder	376 C (188 f/ 188 m) - 232 unaffected first degree family members - 144 HC	rs2253478 rs2396753 rs6980093* rs12533005* rs7799109 rs17137124 rs1456031
FOXP2 contributes to the cognitive impairment in chronic patients with schizophrenia	Lang et al.	2019	China	1106 SCZ (867 completed cognition assessment) (684m/183f)	404 (162m/242f) HC	rs10447760
FOXP2 expression and gray matter density in the male brains of patients with schizophrenia	Sanjuán et al.	2020	Spain	61m SCZ 25m SCZ brain samples 23 RNA	18m HC 11 HC brain samples 25 RNA	rs2396753
Sexual dimorphism in the relationship between Forkhead-Box P2 and BMI with cognitive deficits in schizophrenia	Yang et al.	2022	China	867 (684m/183f) SCZ	402 (158m/244f) HC	rs10447760

Table 1