



# CTLA-4 expression and polymorphisms in Schizophrenia; a systematic review of literature

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Received: 8 July 2023 / Accepted: 29 January 2024  
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## Abstract

Schizophrenia constitutes a severe psychiatric disorder with detrimental impacts on individuals, their support systems, and the broader economy. Extensive research has revealed a notable association between variations in the Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) gene and an increased susceptibility to schizophrenia.

This study represents the first systematic review of the literature investigating the impact of CTLA-4 polymorphisms and expression on the development and progression of schizophrenia.

Our investigation involved a comprehensive search strategy, using a combination of title, abstract, and MESH terms in four databases, including PubMed, Scopus, Web of Science, and Google Scholar, until August 29th, 2023. The complete texts of the identified records were obtained and rigorously assessed based on predefined exclusion and inclusion criteria. Out of the numerous records, a total of 88 were identified through the databases. 10 studies met the criteria; therefore, their quality was assessed and included in this systematic study. The records were then categorized into polymorphism and expression groups. Our investigation emphasizes an association between rs3087243, rs231779, rs231777, rs16840252, rs5742909, and rs231775 polymorphisms and the development of schizophrenia. The results demonstrate a correlation between CTLA-4 polymorphisms and schizophrenia, compelling the need for further research to thoroughly examine the role of CTLA-4 in schizophrenia and other psychiatric disorders.

**Keywords** Schizophrenia · Psychiatric disorders · CTLA-4 · mRNA expression · Polymorphism · Systematic review

## Introduction

Schizophrenia is a debilitating psychiatric disorder that profoundly affects individuals, support systems, and the overall economic landscape due to its substantial detrimental consequences [1]. Typically, this disorder manifests in late adolescence or early adulthood [2, 3], affecting nearly 1% of the world's population [3]. The symptoms of schizophrenia encompass hallucinations and delusions (as positive symptoms), alongside withdrawal, alogia, and flattening (as negative symptoms), coupled with cognitive and thinking challenges [3, 4].

The underlying mechanism of schizophrenia is complex and multifactorial, involving a combination of factors [5, 6]. While a family history of psychiatric conditions is recognized as a major risk factor, it is not necessarily a significant causal factor [5]. Furthermore, within schizophrenia, there is notable variation in the severity of symptoms, the course of the disorder, responses to treatment, and its etiology

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among patients. This inherent heterogeneity gives rise to diverse outcomes in biological investigations [7].

Recently, it has been suggested that autoimmune diseases and severe infections necessitating hospitalization, may contribute to the development of psychiatric disorders like schizophrenia and depression [8–10]. Research indicates elevated autoantibody levels and increased autoantibody reactivity in a subgroup of patients with psychiatric disorders, even in the absence of known autoimmune diseases [11, 12]. Moreover, the prevalence of autoimmune diseases is observed to be higher in patients with schizophrenia and other psychotic disorders [9]. An association between elevated C-reactive protein levels and a higher risk of developing late-onset schizophrenia also has been demonstrated in some studies [13, 14].

Numerous studies have demonstrated T-cell-associated dysfunctions, particularly the dysregulation of T-cell-related cytokines, in both schizophrenia and major depressive disorders [15]. In schizophrenia, lower activation of Th1 (decreased levels of Interferon-gamma (IFN- $\gamma$ )) [16] and higher activation of Th2 (increased levels of interleukin-4 (IL-4), IL-6, and IL-10) [17–19] have been identified. However, in major depressive disorders increased levels of pro-inflammatory cytokines such as IL-1 $\beta$ , tumor necrosis factor alpha (TNF- $\alpha$ ) and IFN- $\gamma$  have been reported [20, 21]. These findings highlight the association between immune system dysfunctions and psychiatric disorders [15]. Moreover, genetic predisposition and variants of immune system genes have also been linked to schizophrenia [12, 22].

The Cytotoxic T Lymphocyte Antigen-4 (CTLA-4) gene, consisting of four exons, is located on the long arm of chromosome 2q33 [23, 24] and has been proposed as a potential candidate gene associated with susceptibility to autoimmune diseases (Fig. 1) [23, 25, 26]. CTLA-4, as an inhibitory molecule, plays a vital role in establishing and maintaining tolerance to self-antigens and regulates the activation of T-cells [15, 27]. It has been found that genetic variations within the CTLA-4 gene may reduce the inhibitory effect on T cells, leading to the onset of various systemic and autoimmune diseases. Examples include insulin-dependent diabetes mellitus (IDDM) and Hashimoto thyroiditis observed in patients with rheumatoid arthritis. Additionally, reduced levels of CTLA-4 have been observed in individuals with autism and Alzheimer's disease [28, 29]. Additionally,

several studies have linked CTLA-4 gene polymorphisms to an increased risk of schizophrenia, a relationship that will be explored in this study. Although several systematic reviews have affirmed the association between the immune system and schizophrenia [29], to our knowledge, none have specifically investigated the role of CTLA-4 expression and polymorphisms in this psychiatric disorder. Therefore, to gain a comprehensive understanding of the roles of CTLA-4 in schizophrenia, we will conduct a systematic review of the literature, examining the influence of CTLA-4 on the development and pathogenesis of schizophrenia, encompassing both gene expression and polymorphisms.

## Methods

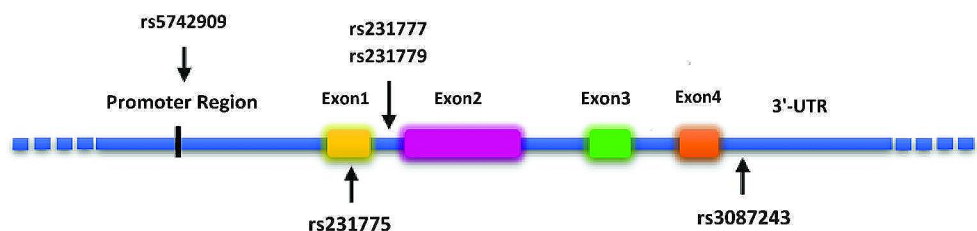
### Literature search strategy

The current systematic review was done according to PRISMA guidelines. A comprehensive search was conducted utilizing a combination of title, abstract, and MESH terms across four databases: PubMed, Scopus, Web of Science, and Google Scholar, up until August 29th, 2023. All selected articles were in English. Additionally, we included references from textbooks and articles to identify potentially eligible studies (Table 1).

### Inclusion and exclusion

We included studies investigating the effect of or association between CTLA-4 antigen and schizophrenia in humans. Additionally, studies examining schizophrenia in conjunction with other psychiatric disorders, such as major depressive disorder and bipolar disorder, were included. No restrictions were imposed on age, ethnicity, duration, gender, or sample size. Since our study investigates the complete role of CTLA-4 in schizophrenia, we included studies related to both polymorphisms (genetics) and expressions (transcriptomics). Notably, this review excludes books, animal studies, and review articles, except for a specific letter directly pertinent to our subject, which is included to enhance the quality of the results. The results from our database search were integrated into Endnote, and duplicate studies were systematically removed. Irrelevant studies

**Fig. 1** The human CTLA4 gene structure and some of the known polymorphisms in schizophrenia



**Table 1** Search strategies

Database	Search strategy	Results
PubMed	((((((((schizophrenia) OR (catatonia)) OR (psychosis)) OR (schizophrenic)) OR (schizoaffective)) OR (schizophreniform)) OR (Dementia Praecox)) OR (schizophrenic disorder)) AND (((((((((CTLA-4) OR (CTLA4)) OR (cytotoxic t-lymphocyte antigen)) OR (CD152)) OR (CTLA 4)) OR (CTLA-4 antigen)) OR (“CTLA-4 expression”) OR (CTLA-4 polymorphism)) OR (CTLA-4 mRNA)) OR (CTLA-4 transcript))	21
Google Scholar	allintitle: (CTLA-4 OR CD152 OR CTLA4 OR “cytotoxic t-lymphocyte antigen 4”) (schizophrenia OR schizoaffective OR schizophreniform OR “dementia praecox” OR schizophrenic OR catatonia)	11
Web of Science	TI= ((CTLA-4 OR CTLA4 OR “CTLA 4” OR “cytotoxic t-lymphocyte antigen 4” OR CD152) AND (schizophrenia OR schizophrenic OR catatonia OR schizoaffective OR schizophreniform OR psychosis OR “dementia praecox”)) ab= ((CTLA-4 OR CTLA4 OR “CTLA 4” OR “cytotoxic t-lymphocyte antigen 4” OR CD152) AND (schizophrenia OR schizophrenic OR catatonia OR schizoaffective OR schizophreniform OR psychosis OR “dementia praecox”))	8 7
Scopus	TITLE-ABS-KEY((CTLA-4 OR CTLA4 OR “CTLA 4” OR “cytotoxic t-lymphocyte antigen 4” OR CD152) AND (schizophrenia OR schizophrenic OR catatonia OR schizoaffective OR schizophreniform OR psychosis OR “dementia praecox”))	41

were removed during the scanning phase when two independent researchers decided on the matching studies until August 29th, 2023.

### Data extraction

Two authors pooled together the results and extracted the data following our protocol, and in case of disagreement, a third author was asked. We extracted the name of the first author, publication year, country of the study, race, sample sizes, including case and control groups, and the results, which were either expressions or polymorphisms.

### Quality assessment

We used a predefined checklist to assess the eligibility of studies. Apart from those doing the data extraction, two other researchers assessed the quality of studies using Joanna Briggs Institute’s (JBI) critical appraisal of evidence Effectiveness tool. The tool has eleven yes/no questions and assesses the study eligibility for systematic reviews [30].

## Results

### Study selection and characteristics

Throughout our search, we obtained a total of 88 studies. Following a thorough duplication check, 38 studies were eliminated due to duplication. Subsequently, the remaining 50 articles underwent assessment based on their titles and abstracts, leading to the selection of 11 studies as the final results after a comprehensive review of both the abstract and full text. One study was excluded as it initially existed as a poster by Frydecka but was later published as a journal article; consequently, only the latter was included in our study. Finally, 10 studies met our criteria, and their quality was assessed before being incorporated into the systematic review.

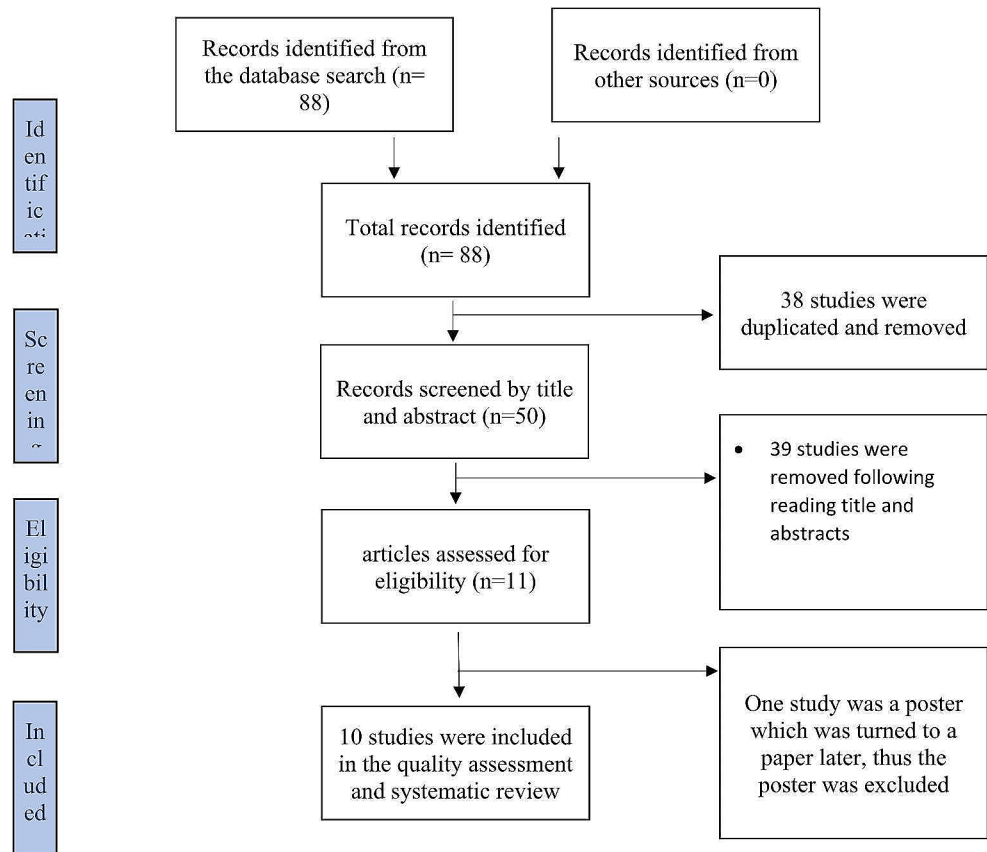
Figure 2 shows the flowchart of our systematic search. The identified studies were subsequently categorized into two groups: polymorphism ( $n=8$ ) and expression ( $n=3$ ), with the study conducted by Kordi-Tamandani [31] falling into both categories. These 10 studies span the publication years from 2001 to 2020. Most studies were conducted in Asia, particularly East Asia, such as Japan, China, Korea, Indonesia, and Iran (Tables 2 and 3), however, one study was conducted in Australia [32]. The only European country investigating the role of CTLA-4 on schizophrenia was Poland [33–35]. The ethnicities predominantly represented in the studies were Caucasian, Chinese, Korean, and Iranian (Tables 2 and 3). In terms of diagnostic tools, one study utilized DSM-V [36], five used DSM-IV [15, 31, 33, 37, 38], one employed DSM-III [32], and two studies utilized both DSM-IV and ICD10 [34, 35]. The diagnostic approach in one study was unspecified [39] (Tables 2 and 3). Two studies investigated the role of CTLA-4 in three disorders, including schizophrenia, bipolar disorder, and major depressive disorders [15, 36].

### Systematic review

The investigation into the role of CTLA-4 was conducted in two stages. Initially, we explored CTLA-4 mRNA expression, and subsequently, we studied CTLA-4 gene polymorphisms.

### CTLA-4 expression

Three studies investigated the expression level of CTLA-4 in schizophrenia [31, 36, 38]. Cai et al. investigated the mRNA expression levels of membrane CTLA-4 (mCTLA-4) and soluble CTLA-4 (sCTLA-4) in peripheral blood mononuclear cells (PBMC) derived from first-episode schizophrenia patients and healthy controls [38]. Their findings revealed a

**Fig. 2** systematic search flowchart**Table 2** Schizophrenia and CTLA-4 expression

First author (year)	Country	Ethnicity	Disorders	Method	Case/control	Source	Diagnostic tool	Results
[38]Cai (2020)	China	Chinese Han	Schizophrenia	Quantitative real-time PCR	65/61	Membrane and soluble CTLA-4 expression in peripheral blood mononuclear cells	DSM-IV	Soluble CTLA-4 expression was reduced in SCZ patients compared to the control group. mCTLA-4 was not different.
[36]Miyamoto (2020)	Japan	N/A	Schizophrenia, bipolar disorder, major depressive disorder	Quantitative real-time PCR using TaqMan probes	50 SCZ, 46 BD, 63 MDD, 159 Control	Peripheral blood	DSM-V	Lower CTLA-4 mRNA expression in blood of SCZ patients vs. healthy control ( $p < 0.001$ )
[31]Kordi-Tamandani (2013)	Iran	Iranian	Schizophrenia	Real-time PCR	17/17	CTLA-4 expression in Peripheral blood cells	DSM-IV	Significantly higher expression of CTLA-4 mRNA levels in patients with SCZ. ( $P < 0.0001$ )

significant reduction in sCTLA-4 expression among schizophrenic patients, while the difference in mCTLA-4 mRNA expression between the control and patient groups remained insignificant ( $p$ -values of 0.009 and 0.769, respectively).

In another study conducted by Miyamoto et al., a lower CTLA-4 mRNA expression was detected in the peripheral blood sample of patients with schizophrenia compared to the healthy control [36]. Conversely, in the study by

**Table 3** Schizophrenia and CTLA-4 polymorphisms

Author (Year)	Country	Ethnicity	Disorder	Method	Case/Control	SNP	Diagnosis	Results
[33] Frydecka (2013)	Poland	Caucasian	Schizophrenia	PCR-RFLP	120/380	rs231775,rs5742909, rs3087243, Microsatellite CTLA-4 g.*642AT (8_33)	DSM-IV	No significant relationship was found between CTLA-4 gene polymorphisms and schizophrenia.
[34] Frydecka (2015)	Poland	Caucasian	Schizophrenia	PCR-RFLP	120/380	rs231775, rs5742909, rs3087243, Microsatellite CTLA-4 g.*642AT(8_33)	ICD-10 and DSM-IV	There were significantly more CTLA4 c.49 A>G[A] alleles and more CTLA4g.319 C>T[T] alleles among patients with co-occurring affective symptoms, compared to the second group of patients.
[32] Jones (2009)	Australia	Caucasian	Schizophrenia	Homogenous MassExtend and iPlex assay	122/122 (81 M/40 F)	rs231775 rs5742909 rs3087243	DSM-III-R	Promoter region SNP (-318 C/T) (rs5742909), and the 3' UTR SNP (rs3087243) significantly associated with schizophrenia in males.
[15] Liu (2011)	China	Chinese Han	Schizophrenia, bipolar disorder and major depressive disorder	PCR	1140 SCZ, 1140 MDD, 1140 BD and 1140 normal Control	rs231775 rs231777 rs231779 rs3087243 rs5742909 rs16840252	DSM-IV	rs231779 conferred risk for schizophrenia, rs231777 and rs16840252 significantly associated with schizophrenia
[37] Jun (2002)	Korea	Korean	Schizophrenia	SSCP	116/149	rs231775	DSM-IV	Significant association of rs231775 with schizophrenia.
[39] Sumirtanurdin (2019)	Indonesia	N/A	Schizophrenia	T-ARMS-PCR	46/51	rs5742909	N/A	No significant association between SNP at rs5742909 (C allele transition to T) with the risk to schizophrenia.
[35] Mak (2018)	Poland	N/A	Schizophrenia	TaqMan SNP genotyping assay	513/347	rs231775	ICD-10 and DSM-IV	No significant differences in distribution of alleles and genotypes between the two groups.
[31] Kordi-Tamandani (2013)	Iran	Iranian	Schizophrenia	T-ARMS-PCR	94/99	rs5742909	DSM-IV	The CT genotype at CTLA-4 -318-C/T polymorphism had a significantly protective effect on the risk to schizophrenia.

Kordi-Tamandani et al., CTLA-4 exhibited higher expression levels compared to the control group [31]. A comprehensive list of study characteristics is provided in Table 2.

### CTLA-4 polymorphisms

Eight studies investigated the polymorphism of the CTLA-4 gene and its association with schizophrenia, as shown in

Table 3. All these studies focused on single nucleotide polymorphisms (SNPs), and two of them were conducted by the same author [33, 34]. Polymorphism of the CTLA-4 gene at position 49 of exon 1 (A/G, rs231775) was the most studied polymorphism (Fig. 1) [15, 32–35, 37]. One study showed a significant association between polymorphisms of rs231775 and the affective symptom domain in schizophrenia [34], suggesting a potential link to the development of the disorder

[37]. rs231779, rs231777, and rs16840252 were also found to be associated with the disease in the Chinese Han population [15]. Additionally, in Caucasian populations, the promoter region SNP -318 C/T (rs5742909) and the 3'-UTR SNP (rs3087243) demonstrated nominally significant associations with schizophrenia, particularly in males [32]. Kordi-Tamandani studied CTLA-4 -318 C/T polymorphism and found the CT genotype had a protective role in terms of schizophrenia risk in Iranian population [31] which was contrary to the results from Sumirtanurdin study which was conducted in Asia [39]. Moreover, Frydecka showed that T allele frequency in the rs5742909 is associated with higher chances of schizophrenia development and is related to worse clinical outcomes [34]. Thus, the polymorphisms that seem to play a role in schizophrenia development, according to the search results, seem to be: rs3087243, rs231779, rs231777, rs16840252, rs5742909, rs231775.

## Discussion

Chronic, low-grade inflammation and T-cell dysfunction have been implicated as risk factors for schizophrenia [38, 40]. The regulatory role of CTLA-4 in T-cell activation and proliferation is crucial, as its deficiency can result in the dysregulation of immune responses and the onset of autoimmunity [38, 41, 42]. On chromosome 2q33, the CTLA-4 gene encodes two distinct isoforms through alternative splicing: the membrane-bound CTLA-4 (mCTLA4) and soluble CTLA-4 (sCTLA4) [38]. While mCTLA-4 mRNA comprises four exons, sCTLA-4 mRNA lacks exon 3 (transmembrane domain) and consists of three exons [38, 43]. Although studies suggest a potential link between CTLA-4 gene variants and susceptibility to schizophrenia, the exact nature of the relationship between CTLA-4 and schizophrenia remains incompletely understood [38].

In this study, the gathered data was divided into two parts: the first part elucidates studies focusing on CTLA-4 expression, while the second part delves into the polymorphisms of the CTLA-4 gene. Two studies reported a significant reduction in CTLA-4 levels [36, 38].

However, a study conducted by Kordi-Tamandani et al. presented a contrary finding, revealing a substantial increase in CTLA-4 mRNA expression among individuals with schizophrenia [31]. Despite Cai's exploration of expression levels related to specific polymorphisms, it did not conclude a direct connection between polymorphisms and the risk of schizophrenia [38]. Consequently, it was only incorporated into the expression section. The increased expression levels in Kordi's study were extremely significant. The difference in results observed within these studies can be due to different study samples. Interestingly, the observed alteration in

expression was influenced by gene polymorphisms, highlighting the importance of investigating CTLA-4 gene polymorphisms within populations affected by schizophrenia [44].

The single nucleotide polymorphisms (SNPs) of the CTLA-4 gene produced controversial results. Several studies identified several CTLA-4-related SNPs, and among them, rs3087243, rs231779, rs231777, rs16840252, rs5742909, and rs231775 were reported in different studies to be associated with schizophrenia.

The SNP CTLA-4 +49 A/G (rs231775), located in the exon 1 of CTLA-4, has been implicated in the development of schizophrenia in several studies [34, 37]. This polymorphism has also been examined in the context of various disorders, contributing to conditions such as systemic lupus erythematosus (SLE), thyroiditis, and malignancies [45–48]. However, investigations into its role in other psychiatric disorders, including depression, have not revealed a significant association [49]. On the other hand, rs231777, rs231779, and rs16840252 demonstrated a notable association with schizophrenia in the Chinese Han population [15]. Nevertheless, the studies exploring these SNPs were limited, necessitating further investigation. Furthermore, the rs5742909 or -318 C/T SNP within the promoter region has been consistently associated with schizophrenia and poor clinical outcomes in multiple studies [31, 32, 34].

In males, rs3087243 demonstrated a significant association with schizophrenia in Caucasian populations [32]. Notably, this SNP has also been implicated in malignancies such as breast, hepatic, kidney, and skin cancer [50].

Several studies attempted to investigate the polymorphisms among schizophrenic population, but the results are inconclusive. A fit of SNPs were found, but their association to schizophrenia differed among studies. This can be explained mainly by the different study population and racial backgrounds, which can highly attribute to genome differences among patients. Large multi-center and multi-national studies are highly needed to illustrate the association between different SNPs and genetic variations and schizophrenia.

In summary, our results imply a connection between multiple polymorphisms in the CTLA-4 gene and schizophrenia. This association is noteworthy not only in the context of schizophrenia but also extends to several other disorders, with a notable presence in neoplasia and immune-related conditions.

## Limitations and future directions

To the best of our knowledge, this is the first systematic review of the role of CTLA-4 in the development and pathogenesis of schizophrenia, which is accompanied by certain limitations. First, it cannot be definitively claimed that the authors have thoroughly studied all published works on the subject of the review. The authors might miss some pertinent works. Second, our review was based on a small number of studies, especially with regard to those investigating the expression of CTLA-4 in schizophrenia. Thus, future studies must evaluate CTLA-4 expression to clarify its contribution to schizophrenia. Third, the included studies did not mention covariates like insulin-dependent diabetes mellitus, Hashimoto thyroiditis, Graves' disease, celiac disease, systemic lupus erythematosus and other autoimmune diseases that might influence CTLA-4 polymorphism or expression, so there can be a confounding bias. Finally, the results are rather heterogeneous. Since high statistical heterogeneity has an essential role in compromising the level of reliability of the results, we could not quantitatively review the studies. Therefore, future studies with homogeneous data are required to access quantitative results and conduct meta-analyses. Since the results have shown that CTLA-4 polymorphisms are associated with schizophrenia, we highly encourage future researchers to evaluate the role of other inhibitory receptors, such as PD-1 and LAG-3, in psychiatric disorders.

**Acknowledgements** The images presented in this paper were prepared using Adobe Illustrator 2023 software.

**Data availability** No Data associated with the manuscript.

## Declarations

**Conflict of interest** The authors declare no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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