Are There Schizophrenia Genetic Markers and Mutations? A Systematic Review and Meta-Analyses

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Abstract

Background: Schizophrenia is a severe psychiatric disorder with a complex genetic factor determining its disease onset. Nevertheless, it is not clear in this mental disorder. Objective: To conduct a systematic review of articles regarding the genetic markers and mutations in schizophrenia. Methods: A systematic review of articles on genetic markers and mutations in schizophrenia, published from January 1, 2011, to September 7, 2015, on SCOPUS database was carried out. Search terms were “Genetic markers”, “Mutation”, and “Schizophrenia”. Results: Of the 527 retrieved studies, 31 met the eligibility criteria. Genetic polymorphism, Immune-associated genes, TCF4 and ZNF804A association with microRNA, Neuregulin gene, Chromosome 13q32 and 11p15.4, genes involved in glutamatergic via schizophrenia and brain structure, appeared to be associated with the origin of schizophrenia. Conclusion: Some studies show genes involved in several pathways leading to the disease pathogenesis such as that one related with the dopaminergic and immune system, or rare alleles. Some genes present no involvement in the etiology of this mental disorder. These findings clarify the genetic complexity of schizophrenia and affirm that together, the genes have an overall effect greater than the sum of the individual effect of each gene.

Keywords

Schizophrenia, Genetic Markers, Mutations, Systematic Review
1. Introduction

Schizophrenia (MIM 181500) is a complex disease that has a lifetime risk of approximately 1% and is characterized by delusions, hallucinations, altered cognition, emotional reactivity and disorganized behavior. Genetic factors account for more than 80% of the variance in susceptibility, and risk likely results from multiple loci of small effect [1] [2]. Supporting evidence has linked the high heritability of schizophrenia (SCZ) to a combination of relatively common alleles of small effect and to a few rare alleles with relatively large effects [3] [4]. Genes like GRIK2, GRIA2, [5] ADAMTS13 [6] and polymorphism present in the MAOA promoter region was associated with schizophrenia [7]. Due to its complex genetic architecture and joint effects among these genes, the overall effect of a gene network is expected to have a greater effect than the sum of individual effect of each gene [8].

Some of the most investigated genes in studies of susceptibility to schizophrenia are those that encode proteins of the dopaminergic system [4]. The dysfunction of the dopamine system is believed to be a fundamental component in SCZ development [9]. Abnormal transmission of dopamine may be involved in the pathogenesis of SCZ [10] [11] [12]. Beyond that, there is compelling evidence that abnormal brain development and disturbed neuroplasticity are major factors in schizophrenia (SCZ) pathology [1] [2] [3] [13].

Also, was found that the genes involved are mainly neural- and immune-related and more likely to interact and take part in the same or related pathways [8]. The abnormal functioning of the immune system including the irregulation and malfunction of different parameters of immune system are strongly associated with pathogenesis of schizophrenia. There is a strong relationship between the clinical characteristics of schizophrenia and disturbances of the immune system [14] [15]. The major histocompatibility complex (MHC), an immune response gene locus chromosome 6, is the most extensively associated locus for schizophrenia in genome-wide association study (GWAS) [16] [17] [18]. However, clinical and genetic heterogeneity and overlapping with other neurodevelopmental disorders complicate our understanding of the etiology of schizophrenia [18].

This research was conducted through a systematic review aiming to identify genetic markers and mutations for schizophrenia. Therefore, this work produces a synthesis of the latest findings about the genetic influence in this mental disorder.

2. Methods

A meta-analyze and systematic review was performed of articles about genetic markers, mutations, and their relations with schizophrenia.

It was conducted a search in the literature through the online database Scopus, in September 2015, by limiting itself to articles published between January 1, 2011 to September 7, 2015. The reason to limit the search between 2011 and 2015 was because during that period there was a significant improvement in the
results of research involving genetic mutations and markers for schizophrenia. Therefore, genetic factors involving schizophrenia had great relevance in the scientific community.

Initially, the search terms browsed in Scopus database were:
#1: “genetic markers” (MeSH term);
#2: “mutation” (MeSH term); and
#3: “schizophrenia” (MeSH term).

Analysis of the article followed predetermined eligibility criteria. The survey was carried out in two phases: 1 AND 2 AND 3, 1 AND 3. It was made for those combinations by using the filter “subject descriptor”. The index utilized was: Title, Abstract and Keywords. We adopted the following inclusion criteria: 1) written publications in English; 2) studies pertaining schizophrenia and mutations or genetic markers; 3) original articles with available full text online; 4) articles that included in the title at least one combination of terms described in the search strategy; and 5) observational (analytical or descriptive, except case reports), experimental or quasi-experimental studies (except animal studies), both prospective and retrospective.

The exclusion criteria were as follows: 1) other study designs, e.g. case reports, case series, literature reviews and comments; 2) non-original studies, including editorials, reviews, forewords, short communications and letters to the editor. Each article was read in its entirety, and the information was entered in a spreadsheet that included authors, year of publication, the study sample description and key data.

Some works found about schizophrenia differed from the proposed theme and were not included because they treat schizophrenia associated with other psychological disorders such as bipolar disorder, by addressing only symptomatic changes or because they are related to disease treatment.

BioEstat 5.0 program was used to calculate the Mantel-Haenszel test and the Odds Ratio (Figure 1) in order to verify the association between the presence of the gene and the chance of developing schizophrenia; the Chi-Square Distribution (Figure 2), which is a probability distribution of the event actually occurs; and the Pearson’s correlation coefficient (Figure 3), which represents the degree of association between certain variables.

The following Figure 1 shows the chances ratio of schizophrenia development associated to the genetic factor.

The following Figure 2 represents the probability distribution according to the associated event.

The following Figure 3 represents the Pearson’s correlation coefficient, which highlights the genetic markers association with the schizophrenia development according its correlation strength.

To better analyze the data, the following stage involved the comparison between the articles and the division of the results obtained from the Reading of each one of them in eight categories: GENETIC POLYMORPHISM (ANNEXIN A5, THBS1, PDLIM5, HDAC, DISC 1 gene, KCNJ3, RGS2, MAOA gene,
Figure 1. Mantel-Haenszel test and odds ratio. Prepared by the authors. The Mantel-Haenszel test and the odds ratio were used in order to calculate the genetic association and the disease establishment. Each set of studies is represented by a line and a square. The former represents the confidence interval and the latter the studies’ effect. The square size represents the importance of each set of studies to the meta-analyses. The vertical line shows the effect absence while the diamond symbolizes the final meta-analysis result. The joint analysis involving all study patients had odds ratio $9.07\ CI\ [8.540 - 9.64]$. This means that if someone has a genetic load compatible with schizophrenia, the chance of developing this disease is 9 times higher.

Figure 2. Chi-square distribution, prepared by the authors. The chi-square distribution was used in order to calculate the probability distribution of the event actually occurs. This involves the freedom degree and it is based on the odds ratio and on the chi-square calculated together and also according to the odds ratio set. With the $p = 0.0430$, the hypothesis of genetic association on the schizophrenia onset is not rejected.

ANKK1, DRD3, GRIK1); IMMUNE-ASSOCIATED GENES (NKAPL, PGBD1, RELA), TCF4 and ZNF804A; ASSOCIATION WITH MICORONA; NEUREGULIN GENE (NRG1, ERBB4); CHROMOSOME 13q32 and 11p15.4; GENES INVOLVED IN GLUTAMATERGIC VIA (PTPN5 gene, GRIN2B, GRIK1, GRIK2, GRIA2, DTNB1 gene, EXYD8); SCHIZOPHRENIA AND
BRAIN STRUCTURE (B3GAT2, ADAMTSL3, DTNBP1 gene); and finally, NEGATIVE RESULTS (PEA15, ENTPD4, GAS2L1, ZIC2, SLC15A1, and FGF14).

3. Results

At first, the aforementioned search strategies resulted in 527 references. After searching the title and abstract of the considered citations for eligibility based on study inclusion criteria, 496 articles were excluded and 31 articles were further retrieved and included in the final sample (Figure 4).

![Figure 3](image)

**Figure 3.** Person’s correlation coefficient, prepared by the authors. The Pearson correlation was used in order to verify the statistical relationship between the genetic variable and the schizophrenia onset. It is a parameter ranging from −1 to 1, in which −1 means a total negative correlation, 0 means no correlation and means 1 overall positive correlation. According to the analysis from the studies, we found a correlation outcome r = 0.79, which shows quantitatively that the schizophrenia development is associated with a genetic marker.

![Figure 4](image)

**Figure 4.** Flow chart showing study selection for the review. Abbreviations: MeSH: Medical Subject Headings.
Articles from SCOPUS database matched the inclusion criteria of the present study. The 31 studies were distributed into the previously determined eight categories as follows: Genetic polymorphism: Boyajyan et al., 2013, Park et al., 2012, Moselhy et al., 2015, Kebir et al., 2014, Cao et al., 2013, Yamada et al., 2012, Gareeva et al., 2013, Sun et al., 2012, Arab et al., 2015, Dai et al., 2014, Norlelawati et al., 2015, (eleven studies), Immune-associated genes, Hashimoto et al., 2012, Zhang et al., 2013, Yu et al., 2014, (three studies), TCF4 and ZNF804A association with microRNA, Zhang et al., 2012, Cattane et al., 2015, (two studies), Neuregulin gene, Naz et al., 2011, ChuanYuan et al., 2011, Ryu et al., 2013, Joshi et al., 2014 (four studies), Chromosome 13q32 and 11p15.4, Gadelha et al., 2012, (one study), Genes involved in glutamatergic via, Gareeva et al., 2013, Pelov et al., 2012, Gareeva et al., 2014, Hirata et al., 2012, Cerasa al, 2012, Zhong et al., 2011, (six studies), Schizophrenia and brain structure, Kähler et al., 2011, Dow et al., 2011, Cerasa et al., 2012, (three studies), Negative results, Saito et al., 2011, Zhang et al., 2012, Gadelha et al., 2012, (three studies). Among the 31 studies, some works were referenced in more than one category. The categorization of studies aims to a better organizational quality systematic review and it is not compulsory that each article must be referenced only in their respective category. Table 1 provides an overview of all studies included in the final sample and of all data elements used during the data analysis process.

4. Discussion

Schizophrenia is a heterogeneous and complex disorder, the etiology of which remains unknown [19]. However, it is considered a complex trait resulting from both genetic and shared environmental etiological influences as reviewed by Sullivan [20]. The genetic contribution to risk is high and heritability estimates based on clinical ascertainment are usually given as over 80% [21] [22] [23] (Figure 5).

4.1. Genetic Polymorphism

4.1.1. Annexin A5 and Apoptotic Processes

It is proposed that both pre and postnatal as well as genetically determined abnormalities of the apoptotic processes might be among factors responsible for the development of schizophrenia [24].

It was shown that annexin A5 coupled to membrane of apoptotic cells is a ligand for C1q protein [25].

The increased levels of annexin A5 and Hficolin in the blood of schizophrenia patients might result from the intensification of the processes of programmed death of cells in the central blood circulation or/and might reflect alterations at the level of neuronal apoptosis due to increase of the bloodbrain barrier permeability in this disorder [26].

The results on genotyping the rs1157945 polymorphism of the annexin A5 gene definitely suggest the association between this mutation and schizophrenia, which enable one to consider the rs1157945*T minor allele of the annexin A5 gene to be a risk factor for disease development [27].
Table 1. Are there schizophrenia genetic markers and mutation? Studies and main findings.

<table>
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<th>Authors and Year</th>
<th>Sample</th>
<th>Main findings</th>
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<tr>
<td>Arab et al. (2015) [4]</td>
<td>120 patients with DSM-IV and PANSS (Positive and Negative Syndrome Scale) assessments of schizophrenia and 100 healthy controls.</td>
<td>Results confirmed previous findings from different ethnic populations, in that the rs1800497 and rs909253 polymorphisms were both associated with risk of schizophrenia. Differences between the genotypes of cases and controls were strongly significant ($P = 0.0005$ for rs1800497 and $P = 0.001$ for rs909253). The relative risk to schizophrenia was 1.2 ($P = 0.01$) for the C allele and 0.8 ($P = 0.04$) for the G allele. The CC, CG, and combined CC/AA genotypes were all more frequent in cases than in controls. These results support an association between ANKK1 and LTA genetic markers and vulnerability to schizophrenia and show the potential influence of just one copy of the mutant C or G allele in the Egyptian population.</td>
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<tr>
<td>Cattane et al. (2015) [74]</td>
<td>A microarray expression study was conducted comparing skin fibroblast transcriptomic profiles from 20 SCZ patients and 20 controls.</td>
<td>This study reports the upregulation of JUN, HIST2H2BE, FOSB, FOS, EGR1 and TCF4 in the fibroblasts of SCZ patients. A significant alteration in EGR1 expression is also present in SCZ PBCs compared to controls and to MDD and BD patients, suggesting that this gene could be a specific biomarker helpful in the differential diagnosis of major psychoses.</td>
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<td>Moselhy et al. (2015) [18]</td>
<td>121 patients with schizophrenia (SCZ) and 170 controls were genotyped using quality controlled primers.</td>
<td>It was found a secondary association between PDLIM5 variants and the paranoid subtype of schizophrenia in Emirati Arabs suggesting that PDLIM5 may represent a determinate/marker for schizophrenia subtype specification. However, no associations were found with variants in PICK1, NRG3 or DISC1 genes.</td>
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<td>Norlelawati et al. (2015) [46]</td>
<td>225 unrelated schizophrenia patients and 350 healthy controls. Schizophrenia cases were collected from the Psychiatry Clinic of Tengku Ampuan Azman Hospital, Kuantan (HTAA).</td>
<td>The study supports the notion that the DISC1 gene is a marker of schizophrenia susceptibility and that rs2509382 in the mutual DISC1 translocation region is a susceptibility marker for schizophrenia among males in Malaysia.</td>
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<td>Dai et al. (2014) [11]</td>
<td>A total of 30 paranoid (15 males and 15 females) and 29 undifferentiated (15 males and 14 females) SCZ patients were collected as cases from Ningbo Kangning Hospital. In addition, 26 age- and gender-matched volunteers in Ningbo Kangning Hospital were enrolled as healthy controls (12 males and 15 females).</td>
<td>Their findings supported that DRD3 gene body hypermethylation was significantly associated with the risk of SCZ.</td>
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<td>Gareeva et al. (2014) [5]</td>
<td>59 males were Russians and 149 (71 females and 78 males) were Tatars. The patients were treated at Republican Mental Hospital no. 1 (Ufa). The mean age was 24.94 ± 8.91 years; the mean age at disease onset, 22.46 ± 7.32 years; and the mean disease history, 3.69 ± 3.85 years.</td>
<td>The findings support the hypothesis that glutamate receptor genes are involved in the etiology and pathogenesis of schizophrenia.</td>
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<td>Joshi et al. (2014) [40]</td>
<td>Postmortem frozen tissues from 30 schizophrenia cases, 7 schizoaffective cases, and 37 well-matched control individuals were provided by the New South Wales Tissue Resource Centre (TRC cohort).</td>
<td>Their findings demonstrate that ErbB4-pan laminar mRNA expression is elevated (layers I, II, V) in schizophrenia. At the cellular level, ErbB4-pan mRNA+ signal was detected predominantly in interneuron-like neurons. They provide evidence from this independent Australian postmortem cohort that ErbB4-JMa expression is elevated in schizophrenia and is linked to deficits in dendrite-targeting somatostatin, neuropeptide Y and vasoactive intestinal peptide interneurons.</td>
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<tr>
<td>Kebir et al. (2014) [41]</td>
<td>Families were included in this study based on the presence of one proband diagnosed with schizophrenia or schizoaffective disorder. The global sample included 951 Caucasian subjects in 313 nuclear families (325 cases and their 626 parents forming</td>
<td>This first exploratory systematic study of the HDAC genes provides consistent support for the involvement of the HDAC3 gene in the etiology of schizophrenia. A statistical epistatic interaction between</td>
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HDAC9, HDAC10, and HDAC11 was detected and seems biologically plausible.

As a result, it was identified one gene set with a joint effect significantly associated with schizophrenia and gene expression profiling analysis suggested that they were mainly neuro- and immune-related genes, such as glutamatergic gene (GRM5), GABAergic genes (GABRB1, GABARAP) and genes located in the MHC region (HLA-C, TAP2, HIST1H1B). Further pathway enrichment analysis suggested that these genes are involved in processes related to neuronal and immune systems, such as the Adherens junction pathway, the Neurotrophin signaling pathway and the Toll-like receptor signaling pathway.

GWAS samples (768 schizophrenia cases and 1733 normal controls) came from individuals of Han Chinese ancestry, genotyped with Illumina Human610-Quad BeadChips.

The results are consistent with those obtained previously and support the hypothesis concerning the association of RGS2 gene polymorphisms with the risk of extrapyramidal syndrome development during haloperidol therapy and their involvement in the etiology and pathogenesis of schizophrenia.

A group of 258 patients diagnosed with paranoid schizophrenia F20.0xx (according to the international classification of diseases ICD10, paranoid schizophrenia in subjects of different ethnic backgrounds) including 110 Russians (50 women and 60 men) and 148 Tatars (68 women and 80 men) undergoing treatment in the Republican Psychiatric Hospital No. 1 of the Ministry of Health of the Republic Bashkortostan participated in the study.

Was observed seven regions yielding linkage signals attaining genome-wide empirical thresholds for suggestive linkage (NPL Z score = 2.78 - 3.49); chromosome 1q26.1 for “non-paranoid delusion factor”, 2p24.3 and 7q31.1 for “prodromal impairment factor”, 1q32.1, 9p21.3, and 9q31.2 for “negative symptom factor”, and 10p13 for “disorganization factor”. Among these loci, chromosome 2p24.3 and 1q32.1 overlap with susceptibility loci of schizophrenia identified in our previous linkage studies. This study suggests the existence of genetic loci related to various clinical features of schizophrenia. Further genetic analyses for these dimensional phenotypes are warranted.

The case samples were 310 random unrelated schizophrenia patients (144 male and 166 female)

Their results provide further evidence for an effect of the DISC1 gene on the etiology of schizophrenia and suggest that STRs in the DISC1 gene may be genetic risk factors for schizophrenia.

The examined subjects are represented by 251 patients with paranoid schizophrenia F20.0xx in accordance with the International Classification of Diseases ICD10 of PS with

In the course of the analysis, this study revealed the following: 1) genetic markers of increased risk of developing paranoid schizophrenia in various ethnic groups, including, in Tatars, the GRIN2B*T/T genotype (p = 0.003; OR = 2.33) and GRIN2B*T allele (p = 0.001; OR = 2.36), rs1805247; in Russians, the GRIN2B*T/T
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<table>
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<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Methods</th>
<th>Findings</th>
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<tr>
<td>Gareeva et al. (2013) [94]</td>
<td>Case-control</td>
<td>1224 patients with schizophrenia (50.9% male (623/601), mean age ± SD: 46.2 ± 15.0 years) and 1663 healthy controls</td>
<td>Brain samples were taken from 35 schizophrenics (26 males, 9 females; mean ± SD age, 42.6 ± 8.5 years; postmortem interval (PMI), 31.4 ± 15.5 h; brain pH, 6.5 ± 0.2), 35 bipolar disorder patients (17 males, 18 females; mean ± SD age, 45.3 ± 10.5 years; PMI, 37.9 ± 18.3 h; brain pH, 6.4 ± 0.3), and 35 controls (26 males, 9 females; mean ± SD age, 44.2 ± 7.6 years; PMI, 29.4 ± 12.9 h; brain pH, 6.6 ± 0.3).</td>
<td>It was genotyped four single-nucleotide polymorphisms (SNPs) in the RELA gene and performed a gene-based association analysis.</td>
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<td>Boyajyan et al. (2013) [27]</td>
<td>Case-control</td>
<td>220 unrelated patients with a DSM-III-R or DSM-IV diagnosis of schizophrenia, as well as for the schizophrenia probands of 108 small nuclear families. Case-control sample and family based sample are completely independent. Each schizophrenia case was matched with a healthy control (N = 211) on the basis of age, ethnicity, and sex.</td>
<td>In the case-control study, the Caucasian subset was 73 of 108 probands (67.5%).</td>
<td>It was found association between ZNF804A and schizophrenia.</td>
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<tr>
<td>Gareeva et al. (2012) [23]</td>
<td>Case-control</td>
<td>22 subjects from 4 families, including 11 patients with schizophrenia and 1 with schizoaffective disorder.</td>
<td>Was analyzed eight SNPs across the GAK1 gene. The marker rs469472 was associated with schizophrenia when we combined the case-control and family samples (p = 0.027).</td>
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<tr>
<td>Zhang et al. (2012) [12]</td>
<td>Case-control</td>
<td>768 patients and 1348 controls. A second sample used 963 patients and 992 controls in the Han Chinese population.</td>
<td>Was analyzed eight SNPs across the GAK1 gene.</td>
<td>Was found association between ZNF804A and schizophrenia.</td>
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<td>Hirata et al. (2012) [104]</td>
<td>Case-control</td>
<td>202 unrelated patients with a DSM-III-R or DSM-IV diagnosis of schizophrenia, as well as for the schizophrenia probands of 108 small nuclear families.</td>
<td>In the study, a single nucleotide polymorphism (SNP) (rs3106653) in KCNJ3, also termed GIRK1 or Kir3.1, is a member of the G protein activated inwardly rectifying K + channel (GIRK) group.</td>
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<tr>
<td>Park et al. (2012)</td>
<td>Case-control</td>
<td>Han Chinese sample comprised of 492 schizophrenia patients and 516 healthy control subjects.</td>
<td>In the study, a single nucleotide polymorphism (SNP) (rs3106653) in the KCNJ3 (potassium inwardly rectifying channel, subfamily J, member 3) gene located at 2q24.1 showed association with schizophrenia. KCNJ3, also termed GIRK1 or Kir3.1, is a member of the G protein activated inwardly rectifying K + channel (GIRK) group.</td>
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<td>Yamada et al. (2012) [47]</td>
<td>Case-control</td>
<td>Two hundred and twenty Korean schizophrenia patients (mean age ± standard deviation, 42.1 ± 10.6 years; male/female = 123/97) and 376 control subjects (44.3 ± 6.3 years; male/female = 192/184) were enrolled for this study.</td>
<td>Was found association between ZNF804A and schizophrenia.</td>
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</tr>
<tr>
<td>Zhang et al. (2012) [71]</td>
<td>Case-control</td>
<td>1224 patients with schizophrenia (50.9% male (623/601), mean age ± SD: 46.2 ± 15.0 years) and 1663 healthy controls</td>
<td>Was analyzed eight SNPs across the GAK1 gene.</td>
<td>Was found association between ZNF804A and schizophrenia.</td>
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It was shown that the pathogenesis of schizophrenia is characterized by an increased rate of apoptosis, which is more pronounced in the case of the first-episode neuroleptic-free patients than in the case of chronic patients that receive typical neuroleptic haloperidol. It was also shown that the rs11575945 polymorphism of the annexin A5 gene is associated with schizophrenia, and its minor allele is responsible for higher levels of the annexin A5 protein in the blood and represents one of the risk factors for the development of this disease.
Hashimoto et al. (2011) [70]

(46.5% male (773/890), mean age ± SD: 46.9 ± 20.7 years).

Zhong et al. (2011) [2]

576 individuals diagnosed with schizophrenia (290 males, mean age = 35.3 ± 11.6; 286 females, mean age = 32.7 ± 13.4) and 566 healthy control subjects (308 males, mean age = 29.1 ± 13.6; 258 females, mean age = 29.4 ± 13.4). All patients were diagnosed by the Psychiatry Department of the Affiliated Hospital of Xi’an Jiaotong University School of Medicine according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for schizophrenia.

Naz et al. (2011) [15]

Schizophrenia patients and in controls. One hundred patients with schizophrenia and 70 healthy controls participated in the present study.

ChuanYuan et al. (2011) [19]

81 Chinese Va schizophrenic patients and 210 Chinese Va healthy subjects

Pelov et al. (2011) [98]

868 Israeli Jewish participants, of whom 286 were patients with SZ and 582 were healthy controls. SZ patients were included with information regarding ethnicity (Ashkenazi vs. non-Ashkenazi origin).

Dow et al. (2011) [6]

Whole blood samples were randomly selected from 92 schizophrenia patients from both the Munich and Aberdeen subjects.

Cerasa et al. (2011) [102]

One hundred and seven healthy individuals (Caucasian, age-range: 18 - 73) recruited from universities, community recreational centers and hospital personnel from 2005 to 2009.

Saito et al. (2011) [120]

Subset of subjects (94 schizophrenia patients and 94 control subjects).

Sun et al. (2011) [7]

555 unrelated patients with paranoid schizophrenia and 567 unrelated healthy controls. A second sample analyzed 73 drug-free patients.

Kähler et al. (2011) [13]

Norwegian subset (98 cases; 177 control subjects) with structural magnetic resonance imaging data.

It was examined the association between the neuregulin 1 and tumor necrosis factor-α (−308) gene polymorphism with schizophrenia. This association was performed on the basis of molecular biology to screen the mutations of neuregulin 1 and tumor necrosis factor-α (−308) gene in schizophrenic patients by polymorphism analysis. Statistical analysis of the observed data shows that there was an association (P = 0.003) between patient’s group and controls in terms of genotypes of single-nucleotide polymorphism 1 rather than single-nucleotide polymorphism 2 of neuregulin 1.

The results imply a model in which PTPN5 may play a role in normal cognitive functioning and contribute to aspects of the neuropathology of SZ.

The study fails to provide evidence for the contribution of PEA15, ENTPD4, and GAS2LI genes to the etiology of schizophrenia in the Japanese population.

Haplotypic association was found for the VNTR-rs6323, VNTR rs1137070, and VNTRrs6323-rs1137070 haplotypes in female subjects. Nevertheless, no significant change of the expression of MAOA mRNA was detected in either female or male patients with paranoid schizophrenia.

The present results suggest that effects on biosynthesis of the neuronal epitope HNK-1, through common B3GAT2 variation, could increase the risk of SCZ, possibly by decreasing cortical area.
4.1.2. Synaptic Regulation and Schizophrenia

Recently, thrombospondin 1 (THBS1) was discovered to be the essential astrocyte-derived synaptogenesis-promoting factor, and has been shown to contribute to the repair of brain injury through its assistance and promotion of neurogenesis [28] [29] [30].

Another work reported a gene PDLIM5 that is localized to the postsynaptic density where it has an important role in limiting the size of dendritic spines—the small synaptic protrusions that serve as the primary sites of excitatory synaptic transmission in the CNS [31] [32].

THBS1 is a 16.39 kb gene located on chromosome 15q15. The chromosome 15q15 region has been reported to be a susceptibility locus on schizophrenia [33] [34] [35], and clinical symptoms of schizophrenia such as periodic catatonia [33] [34].

PDLIM5 was found to be a significant secondary predictor of the paranoid subtype of schizophrenia in this Emirati Arab cohort [18].

Little is known about the biological function of THBS1 in the brain or in schizophrenia. However, given the involvement of astrocytes in the pathogenesis of schizophrenia, and the role of THBS1 in synaptic alteration, it is speculated that THBS1 may be a candidate gene involved in schizophrenia [33] [34] [35].

The finding here of PDLIM5 as a potential marker of schizophrenia subtype expands the role of synaptogenesis in neuropsychiatric disorders more generally [36] [37].

4.1.3. HDAC (Histone Deacetylases)

Several studies suggest the involvement of HDAC dysfunction in major psychotic disorders. First, mRNA expression levels of GAD67 in the prefrontal cortex of patients with schizophrenia were found to be strongly and negatively cor-
related with mRNA expression levels of \( HDACs \) 1, 3, and 4 [38]. In the same way, a common variant in \( HDAC3 \) region and epistatic interactions between \( HDAC9, HDAC10 \) and \( HDAC11 \) genes were found associated with schizophrenia. Second, \( HDAC \) activity has been found to be enhanced in the prefrontal cortex of patients with schizophrenia [39].

Given that \( HDAC \) proteins interact and form multiprotein complexes [40], and that a \( HDAC \) protein seldom operates alone, was tested that epistatic interaction between polymorphisms of \( HDAC \) genes may confer an increased risk of schizophrenia [41].

### 4.1.4. **DISC1 Gene**

Mutant \( DISC1 \) is proposed to contribute to schizophrenia susceptibility by disrupting intracellular transport, neurite modeling, neuronal migration, and proper development of the cerebral cortex [42] [43] [44]. A study found three highly polymorphic STR loci in introns 1, 8, and 9 of the \( DISC1 \) gene and identified two novel loci, including \((ATCC)n1\) and \((ATCC)n2\). The three STRs showed a significant association with schizophrenia. It is noteworthy that the allele distribution of D1S1621 showed a higher risk of schizophrenia [45].

Another study found two SNPs (rs4658971 and rs1538979) to be significantly associated with schizophrenia in terms of both genotypes and allelic distribution. Additionally, it was found an association of rs2509382 with schizophrenia among male participants [46].

### 4.1.5. **Gene Association Involved with G-Protein and Schizophrenia**

In the research of Yamada et al. [47], a gene found is the \( KCNJ3 \), also known as \( GIRK1/KIR3.1 \). This gene is a novel candidate gene for schizophrenia. The gene encodes a G protein-activated inwardly rectifying potassium channel (\( GIRK1/KIR3.1 \)) and belongs \( KIR3.X \) the subfamily of potassium rectification inside channels. In that study, a single nucleotide polymorphism (SNP) (rs3106653) in the \( KCNJ3 \) (potassium inwardly rectifying channel, subfamily J, member 3) gene located at 2q24.1 showed association with schizophrenia in two independent sample sets. Moreover, experiments real-time quantitative RT-PCR showed that \( KCNJ3 \) is regulated in the prefrontal cortex schizophrenic patients. Decreased gene expression was observed in the brains from bipolar disorder, as well as schizophrenia patients. This finding may lend support to the “hypo-NMDA theory of schizophrenia” [47].

In this way, any research groups are investigating the gene family of regulators of G-protein signaling (RGSs) because these genes modulate signal transduction via multiple neurotransmitter receptors (i.e., dopamine, glutamate, serotonin, and \( \gamma \)-aminobutyric acid) involved in the pathogenesis of schizophrenia [48] [49] [50] [51] [52].

Associations between several polymorphisms of the \( RGS2 \) gene and the severity of schizophrenia were identified in patients by data show that the \( RGS2^*G^*G^*T^*C^*T^* \) haplotype for the rs2746071, rs2746072, rs2746073, rs4606, and rs3767488 polymorphisms of the \( RGS2 \) gene is a genetic marker of increased
risk of schizophrenia in Russian and Tatar residents of the Republic of Bashkortostan. Furthermore, the \(RGS2^*G/\!*G\) genotype and the \(RGS2^*G\) allele of the polymorphic rs2746071 locus of the \(RGS2\) gene are risk factors for the development of schizophrenia in Russians and Tatars. The \(RGS2^*A/\!*A\) genotype, the \(RGS2^*A\) allele of the polymorphic rs2746071 locus of the \(RGS2\) gene, and the \(RGS2^*A^*G^*T^*C^*T\) haplotype (rs2746071, rs2746072, rs2746073, rs4606, and rs3767488) of the \(RGS2\) gene are protective with regard to the risk of developing paranoid schizophrenia in Russians and Tatars [52].

The conclusion from their study is consistent with results obtained previously, and supports the hypothesis concerning the association of polymorphisms \(RGS2\) gene involvement in the etiology and pathogenesis of schizophrenia [52].

4.1.6. Dopamine Association with Schizophrenia

Dopamine neurons in the substantia nigra are key neurotransmitters in human brain that contribute to the pathogenesis of SCZ [53].

The “dopamine-serotonin” imbalance hypothesis of schizophrenia claims that disruption in cortical-subcortical dopamine and serotonin neurotransmission may play an important role in the pathogenesis of schizophrenia [7] [54].

Monoamine oxidase A (MAOA) is the enzyme responsible for degradation of several monoamines, such as dopamine and serotonin that are considered as being two of the most important neurotransmitters involved in the pathophysiology of schizophrenia [7]. In a study of Chinese population, all the informative SNPs and the VNTR polymorphism within the MAOA gene were screened. The present results suggest that haplotypes VNTR(L)-rs6323(T), VNTR(L)-rs1137070(C), and VNTR-(L)-rs6323(T)-rs1137070(C) may be associated with the increased risk of paranoid schizophrenia in female subjects [7]. Other genes also investigated in susceptibility studies schizophrenia are those encoding proteins the dopaminergic system [4].

One such gene is the rs1800497 singlet nucleotide polymorphism (SNP) It was identified in exon 8 of repetition and Ankyrin kinase domain containing 1 gene (ANKK1) (MIM 608774) only 10 kb away from D2 (DRD2) dopamine receptor gene (located on 11q23.2, MIM 126450) in the 3’untranslated region. This polymorphism which leads to a substitution glutamic acid to lysine base (E713K) that can high-specificity substrate binding [55] probably modulates the function and expression of DRD2 due to its proximity [56]. Despite the fact that the SNP rs1800497 is located ANKK1 the gene appears to be in linkage disequilibrium with several genetic variants DRD2, which could potentially explain a dopaminergic role in the pathogenesis of schizophrenia [4] [57].

Dai et al. [11] demonstrated that the DRD3 gene methylation, subtype of the dopamine receptor family, may have the potential to serve as a gender-specific biomarker to monitor the risk and development of schizophrenia.

4.2. Immune-Associated Genes

In recent years, the extended MHC region has been implicated as a main factor in schizophrenia pathogenesis, supported by GWASs of schizophrenia in differ-
ent populations [16] [58] [59] [60] [61] [62]. Products of the MHC region implicated in the pathogenesis of schizophrenia not only contribute to immune responses but also have general functions in different molecular biological processes [62] [63]. Numerous other genes in the extended MHC region have been shown to be involved in the pathogenesis of schizophrenia. MICB, HLA-A, and HLA-B are classic MHC molecules that play central roles in the development of host defense and immunity [62] [64] [65].

In fact, more and more evidence suggested immune-related genes may play important roles in schizophrenia [8]. For example, several GWAS revealed that many immune genes are significantly associated with schizophrenia [8] [59] [66] [67]. In a replication study, all six SNPs within the NKAPL and PGBD1 genes displayed an association with schizophrenia, but neither of the two SNPs in the ZKSCAN4 gene showed an association [62].

Furthermore, study evidence was found that genetic variants of the RELA gene are associated with the risk for schizophrenia. The v-rel avian reticuloendotheliosis viral oncogene homolog A (RELA) gene encodes the major subunit of the NF-kB protein complex, are abundantly expressed in neurons and glia [68]. The NFKB3 located on chromosome 11q13 showed a suggestive linkage to schizophrenia in a family-based linkage disequilibrium analysis in a Japanese population [69].

A GWAS study in Caucasian population showed significant association with schizophrenia were in a region of LD on chromosome 6p22.1, including several immunity related genes other than the RELA gene [69]. However, the biological significance of this gene in susceptibility for schizophrenia might not be large, because 22% of the patients with schizophrenia have homozygous of risk allele in SNP4, but 16% of the controls also are homozygous of risk allele in SNP4. At the same time, the association between the RELA gene and schizophrenia might explain, at least in part, the relation between immune system and schizophrenia [70].

The results not only provide further evidence that schizophrenia is a complex disease involving immune systems [16] [58] [59], but also indicate that the resultant genes identified in the modules are expressed in brain tissues, suggesting these genes may play important roles in brain function [8].

4.3. TCF4 and ZNF804A Association with microRNA

The most recent GWAS of schizophrenia identified five new association loci and the strongest new finding was with rs1625579 (P = 1.6 × 10 −11) within an intron of a putative primary transcript for miRNA137, a known regulator of neuronal development [66] [71]. In addition, the TCF4 gene is target of several microRNAs, including the mir-137, which was implicated in SCZ etiology in GWAS studies [72]. In particular, the SCZ-associated rs1625579 SNP in miR-137 was correlated with the decreased expression of this microRNA in the dorsolateral prefrontal cortex and a consequent increase in TCF4 levels [73] [74]. In another analysis was suggested that ZNF804A may link miRNA137 to
the specific molecular pathways or cellular processes implicated in schizophrenia, and experimental evidences were warranted to confirm the direct action between miRNA137 and ZNF804A. It has been suggested that the dysregulation of some miRNAs could be involved in the pathophysiology of schizophrenia [71] [75] [76].

4.4. Neuregulin Gene

Two critical neurodevelopmental genes that have been linked to schizophrenia susceptibility are neuregulin 1 [77] \( (NRG1, 8p22-p11) \) [19] and its receptor \( ERBB4 \) [77] [78] [79] [80].

It is possible that elevated levels of cleaved \( ECTO-ERBB4 \) may neutralise the membrane-bound \( CRD-NRG1 \) (encoded by \( NRG1 \)-Type III synthesized by pyramidal neurons) resulting in reduced cross-talk between \( NRG1 \) and \( ERBB4 \). Importantly, \( NRG1-ERBB4 \) signaling has been shown to be important for the development of inhibitory circuits, and a reduction in \( NRG1-ERBB4 \) cross-talk does result in reduced molecular markers of inhibitory synapses [81] [82].

Alternatively, elevated levels of cleaved \( ECTO-ERBB4 \) may result in increased \( NRG1 \) backward-signaling, and in turn, altered gene expression in schizophrenia. This observation is consistent with their previous findings linking the schizophrenia-associated \( HAPICE \) risk haplotype [80] with increased \( NRG1 \)-Type III mRNA expression [83], and their earlier observations of increased cytoplasmic \( NRG1-ICD \) in schizophrenia [77] [84].

Moreover, Chen et al. [85] found strong evidence of association between “delusion factor” and SNPs of Neuregulin3 (\( NRG3 \)) on chromosome 10q22-q23, a region identified in their previous genome-wide linkage analysis of schizophrenia [86].

4.5. Chromosome 13q32 and 11p15.4

Blouin et al. [87] reported a non-parametric linkage (NPL) analysis providing significant evidence for an SSL on chromosome 13q32 (NPL score = 4.18; \( p = 0.000002 \)), and suggestive evidence for another SSL on chromosome 8p21-22 (NPL = 3.46; \( p = 0.0001 \)). In the study was founded suggestive evidence for linkage on chromosomal regions 13q32 and 11p15.4 under the criteria of Lander and Kruglyak [88].

Brzustowicz et al. [89] analyzed 21 Canadian families with schizophrenia and found genome-wide significant LOD scores on 13q. Brzustowicz et al. [90], using the same dataset and multipoint analysis and found a maximum LOD score of 3.81 with an empirical \( p = 0.02 \) under a recessive-broad model of schizophrenia at D13S793, with an estimated 65% of families linked to this region.

Some more recent studies found evidence for a role of chromosome 11p15.4 in bipolar disorder [91], autism [92] and attention deficit hyperactivity disorder [93]. This relative lack of previous evidence for chromosome 11p15 contrasted with the strong previous findings available for 13q32 [23].

Thus, although they should not disregard the linkage with 11p15.4, their pri-
primary finding is an additional evidence for a potential role for 13q32 region in a small Brazilian sample of families with early onset schizophrenia affected individuals. The allele-sharing model tested is compatible with allelic homogeneity within the families [23].

4.6. Genes Involved in Glutamatergic Pathway

Hypoglutamatergic hypothesis, which postulates disturbances in the glutamate neurotransmitter pathway, is one of the neurochemical hypotheses of schizophrenia pathogenesis, which in recent times, has attracted attention from researchers [94].

There is considerable evidence suggesting the involvement of ionotrophic glutamate receptors in SCZ [95] [96].

Changes in affinity of glutamate receptors, transcription of their genes, and expression of their subunits in the prefrontal cortex, hippocampus, and thalamus have been revealed in schizophrenics in post mortem studies [97].

In a study, was examined the association of the protein tyrosine phosphatase non-receptor 5 (PTPN5) gene, which encodes for Striatal-enriched protein tyrosine phosphatase (STEP), with both schizophrenia and cognitive. The variants of protein tyrosine phosphatase non-receptor 5 (PTPN5), the STEP encoding gene involved in glutamate receptor trafficking, are associated with both the diagnosis of SCZ and with neurocognitive function in general [98].

The GRIN2B gene encoding the subunit NR2B NMDA glutamate receptor and its association with schizophrenia was studied in Russians and Tartars, yielding positive results [94].

In genetic studies, previously, they have found some evidence which is components of the glutamate system, namely the GRIN2B gene [99].

Another gene involved in the modulation of glutamatergic transmission is the dystrobrevin-binding protein 1 (DTNBPI) gene, known to the dysbindin gene is located in chromosome 6p22.3 [100] [101] [102].

In fact, in primary cortical neuronal culture, dysbindin appears to influence exocytotic glutamate release via upregulation of molecules in presynaptic machinery [100] [102].

The GRIA2 ionotropic glutamate receptor gene consists of 16 exons and 15 introns and codes for the GluR2 subunit of the AMPA glutamate receptor [5].

The GRIK1 gene (glutamate receptor ionotropic kainate-1) is located on human chromosome 21q22 with 18 exons [103] [104].

The GRIK2 gene codes for subunit 2 of the kainate glutamate receptor and includes 17 exons. The gene is expressed in the granular layer of the cerebellum, the dentate gyrus of the hippocampus, and the neocortex [5].

The results point to potential involvement of GRIK1 in Caucasian schizophrenia patients [104].

It is also known that GRIK2 (6q1621) and GRIA2 (4q3233) are in schizophrenia linked chromosome regions [5] [105] [106].

From a functional perspective, FXYD6 is a member of the FXYD protein fam-
ily. All members of this family have been shown to modulate Na, K-ATPase and have long-term physiological importance in maintaining cation homeostasis [107].

Interestingly, Na, K-ATPases and glutamate (the major excitatory neurotransmitter in the mammalian brain) are part of the same macromolecular complex and operate as a functional unit to regulate glutamatergic neurotransmission [2] [108].

Zhong et al. [2] reported that the G allele of rs11544201, located in the third exon of FXYD6, is a compelling risk factor for schizophrenia in Han Chinese.

4.7. Schizophrenia and Brain Structure

Cognitive deficits are a core feature in SCZ [109], and brain structural changes such as reduced hippocampal and cortical volume [110], the extracellular matrix (ECM) abnormalities [111], as well as reduced cortical thickness [112] have been reported in SCZ patients.

The neural ECM has a specific molecular composition, with chondroitin sulfate proteoglycans (CSPGs) organised as perineuronal nets (PNNs), enveloping neuronal soma and dendrites [111].

The Human Natural Killer-1 (HNK-1) carbohydrate is among the most characteristic glycoepitopes in the nervous system, involved in neural crest cell migration, neurite outgrowth, neuronal cell adhesion, and synaptic plasticity [113] [114]. Kähler et al. [13] suggest that effects on biosynthesis of the neuronal epitope HNK-1, through common variation in B3GAT2, might decrease cortical surface area and thus increase the risk of SCZ.

ADAMTSL3 is a member of the ADAMTS superfamily of proteins, encompassing the 19 human ADAMTS metalloproteases and the seven non-proteolytic ADAMTS-like proteins [6].

ADAMTSL3 itself has been shown to be an important ECM component [115].

Considering the known biology of other superfamily members in the neural ECM, we propose that ADAMTSL3 could plausibly be involved in the PNN abnormalities seen in schizophrenia [111].

Meanwhile, the dysbindin (dystrobrevin-binding protein 1) gene has been indicated as one of the most important schizophrenia susceptibility genes. The dystrobrevin-binding protein 1 (DTNBP1) gene, known as the dysbindin gene, is located in chromosome 6p22.3, encodes 40 - 50 kDa protein, which is widely expressed in neurons of the human brain, and plays a significant role in modulating glutamatergic neurotransmission [100] [101]. Recently, the C-A-T haplotype (derived from SNPs rs2619539, rs3213207 and rs2619538) reported by Williams et al. [116] has shown a strong association with schizophrenia, reduced dysbindin mRNA expression in human post-mortem analysis of homogenized human brain [117], poorer cognitive performance in working memory [118] and reduced gray matter volume in the prefrontal cortex in patients with schizophrenia [102] [119].
4.8. Negative Results

In the study of genes that give the scenario susceptibility to schizophrenia, some genes were tested, and there were no satisfactory results, like PEA15 genes, ENTPD4, Genes GAS2L1 [120] and COMT [12]. The PEA15 gene is located at 1q21.1, the gene is ENTPD4 on 8p21.3 and GAS2L1 gene is in 22q12. These three genes are homologous [120]. The COMT gene is located at 22q11.2, which is a region that has been implicated in linkage areas of SCZ [12] [121].

This single-nucleotide polymorphism (SNP) has been widely studied for its connection with SCZ susceptibility, but with conflicting results [120]. Saito et al. [120] suggests that PEA15 and GAS2L1 do not play an important role in susceptibility to schizophrenia in the Japanese population. Saito et al. [120] left ENTPD4 out of further analysis beyond the screening scan sample subset, since high P values for allelic frequencies suggest that this gene is also unlikely to be related to schizophrenia.

Other genes have also been investigated in schizophrenia with predominantly negative results are ZIC2, SLC15A1, and FGF14 [23] (Figure 6).

However, further research on these genes which are located on schizophrenia susceptibility loci, using different SNP’s and a large sample set will be required [120].

5. Strengths

This study involves a search for genetic risk markers for Schizophrenia; Besides, a meta-analysis of studies was carried out, allowing a better understanding and a more precise analysis of the relation of genetic changes and Schizophrenia onset. Most of the analyzed studies have shown an association, in a greater or lesser level, with Schizophrenia. Moreover, there is a need for more meta-analyses of studies on this topic in the literature.

6. Limitations

Through this analysis it was not possible to determine what kinds of genetic
changes presented a higher risk to the schizophrenia development. Besides, the sample size was restricted due to the inclusion criteria.

7. Conclusion

This study shows numerous genetic targets have been identified related to susceptibility to schizophrenia. Great steps have been taken on this theme, but there is still a real need for more detailed studies like ours, addressing this same topic with a larger sample, in view of that the existence of genetic markers and mutations for SCZ is still controversial. Thus, gathering these markers and mutations already set to develop studies with this approach will enable the prevention, diagnosis and more targeted treatment for patients with schizophrenia, improving their quality of life.

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Conflict of Interest

The authors declare no conflict of interest.

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