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Systematic Review

ZNF804A variants relation to schizophrenia: a systematic review

Ahmed M. Alsheikh*

Department of General Practitioner, Dr. Abdullrahman Almishari Hospital, Riyadh, Saudi Arabia

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***Correspondence:**
Dr. Ahmed M. Alsheikh,
E-mail: AhmedAlsheikh96@hotmail.com

ABSTRACT

Schizophrenia is a devastating mental disease; its etiology isn't clearly understood. However, several hypotheses have been suggested; one of them is the involvement of the genetic factor. Rare and common variants of deoxyribonucleic acid (DNA) genes may contribute to the development of schizophrenia. ZNF804A is a gene encoding for zinc-finger protein, which has been reported to be associated with schizophrenia. However, a few recent studies were conducted on such subject, and there was no systematic analysis for such association. This study assessed the relation between ZNF804A variants and schizophrenia by reviewing the previous studies concerned with such subject. This systematic review was according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist guidance for systematic review includes Pubmed, Embase, and Medline databases were used for searching for published articles between 2015 and 2021. The inclusion criteria were original articles conducted on schizophrenia patients, English, and full text- articles. As well as study the association between SCZ and ZNF804A variants. A total of 408 articles were obtained, only six articles were eligible for the inclusion criteria. The included studies involved a total number of 4,579 of them there were 2,738 schizophrenia patients and was conducted on four populations. All studies reported rs1344706 of the ZNF804A gene. The association between rs1344706 of the ZNF804A gene and SCZ was found in four studies out of the six studies, whereas the other two studies didn't find such association. The association was concluded by the significant increase in the frequency of genotype and allele (A) among SCZ patients. ZNF804A gene variant at the rs1344706 was associated with the etiology of schizophrenia, with the A allele being the risk allele for the disease development.

Keywords: ZNF804A Gene, rs1344706, Polymorphism, Schizophrenia, Correlation

INTRODUCTION

Schizophrenia (SCZ) is a severe neuropsychiatric disease with a complex etiology; its global lifetime prevalence is almost 1% and remains a significant public health problem.[1] The mean SCZ features include various psychotic symptoms such as auditory hallucinations, disorganized behavior, delusions, cognitive impairment, social isolation, and altered emotional reactivity.[2]

One of the multiple hypotheses for the etiology of SCZ is the role of the genetic component in addition to other environmental and developmental factors that have been consistently demonstrated by family, twin, and adoption studies.[3,5] Strong evidence has been identified regarding the genetic role in SCZ etiology started from the early linkage and association analyses to the recent large-scale genome-wide association studies (GWAS).[6]

One example is the first genetic variant that achieved the genome-wide level of statistical significance in SCZ GWAS; this genetic variant is at the restriction site (rs) 1344706 in zinc-finger protein 804A, which is abbreviated as ZNF804A.[7] ZNF804A is located on chromosome 2q32.1 and has three introns and four exons.[8] ZNF804A encodes zinc finger protein 804A, which contains a C2H2-type zinc finger domain; it is distributed throughout the

brain of a human, particularly in the brain cortices and the developing medial temporal lobe.[9,11]

Several studies reported the association between SCZ and the intronic single nucleotide polymorphism (SNP) at rs1344706 (A/C), where the A allele is the risk allele.[7,8,12,13] Although there is substantial genetic evidence and preliminary understanding of the neuronal and molecular mechanism of the ZNF804A risk allele in SCZ susceptibility, there is a lack of systematic synthesis of the current evidence to depict the potential use of this gene in future prevention and therapies.[6] There was one meta-analysis in 2014 and included studies published until 2013 [14], and the review included studies until 2016, but there was no systematic review that included articles published recently.[6] So, this systematic review was performed to identify the association between ZNF804A variants and SCZ and try to predict its usefulness in predicting SCZ for protection against SCZ. Hence, we conducted this systematic review by revising and reviewing the previous studies conducted on the current subject.

METHODS

Writing this systematic review was according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist guidance for systematic review.[15] Three electronic databases were revised, including Pubmed, Embase, and Medline databases, to select eligible research articles between the year 2015 and the year 2021.

Various keywords were used for searching purposes, including "schizophrenia or gene variants or SNP or rs134406 or ZNF804A or association or correlation." All the titles and abstracts produced from this primary exploration were revised thoroughly to prevent missing potential studies.

Eligibility criteria

All the titles and abstracts produced from this primary exploration before 2015 were excluded. The remaining findings were then examined to choose only original research articles that reported the association between SCZ and ZNF804A variants. All articles conducted on SZC patients and reported ZNF804A gene variants were eligible. Only articles in English were included, whereas articles written in other languages were excluded.

The second step was the determination of the inclusion criteria to select the eligible studies. Abstracts were revised manually to select the relevant articles for this review. The inclusion criteria were: original studies conducted by SCZ patients, written in the English language, and full-text articles. Studies that had incomplete or overlapped data, unavailable full-text articles, duplicated articles, and review articles were excluded. The full description of the search strategy is shown in Figure 1.

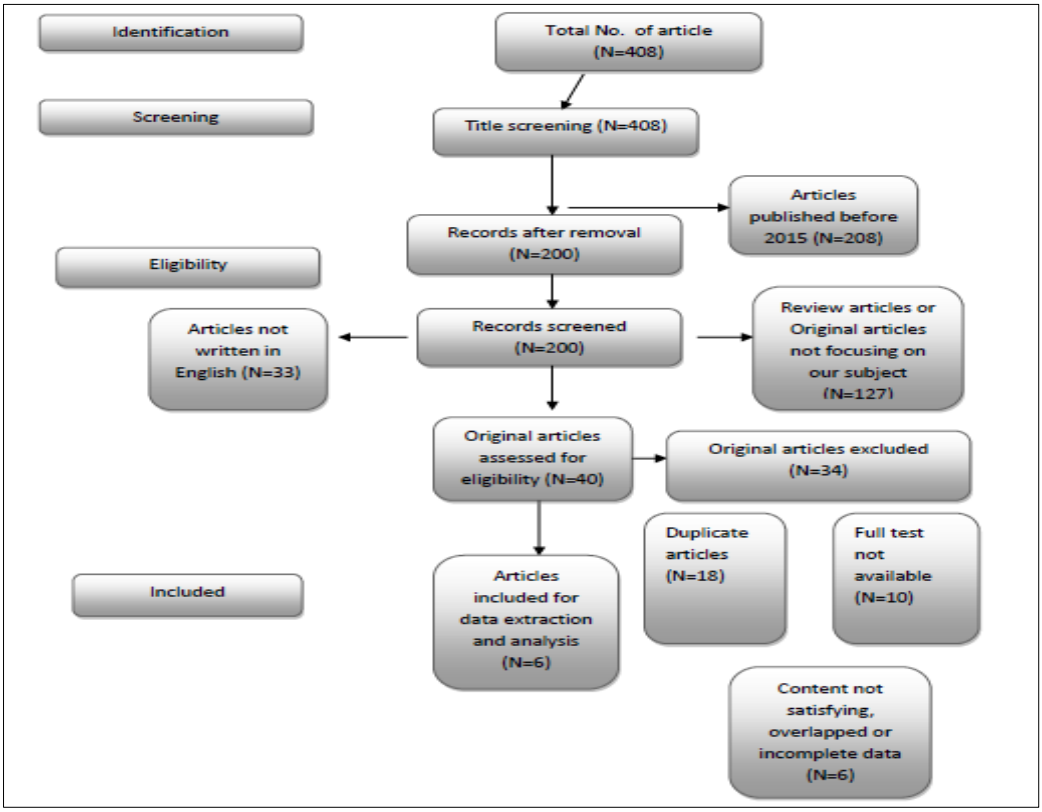

Figure 1: Planning of eligible criteria.

Table 1: Characteristics of reviewed articles.

Author and publication year	Publi-shed	Study design	Sam-ple size (N)	Sample popula-tion	Genetic analysis method	Methodology
Anguiano et al[16]	2021	A cross-sectional study	860	Mexican	TaqMan SNP genotyping	The participants sorted to two groups; Patients diagnosed with SCZ, BPD, SAD=228 and Control group=295. As well as conducted to 167 patients and 170 controls for identification of rare and common variants
Zhou et al[17]	2021	A cross-sectional study	160	Chinese	PCR genotyping	The participants sorted to two groups; the imaging data were preprocessed by PANDA software and calculated the fractional anisotropy of 60 SCZ patients and 100 healthy individuals
De Castro-Catala et al[18]	2017	A cross-sectional study	706	Non-European	TaqMan assay for genotyping	Assessed the positive schizotypy and positive psychotic-like experiences among 706 participants
Wang et al[19]	2016	Case-control study	2274	Han Chinese	LDR-PCR for genotyping	Clinical case study of 1284 SCZ and 990 healthy cases
Mallas et al[20]	2016	A cross-sectional study	460	UK	TaqMan assay for genotyping	Genotyped for the rs1344706 SNP and DTI of 63 SCZ, 43 BPD, 124 control cases
Wei et al[21]	2015	A cross-sectional study	119	Chinese	PCR genotyping	Genotyped of 59 unmedicated first episode SZ and 60 healthy controls for the ZNF804A SNP rs1344706 cases, and examined of cortical thickness, surface area, and cortical volume

Table 2: Objectives and results of reviewed articles.

Author and publication year	Objective	Targeting gene	Results and main findings
Anguiano et al 2021[16]	To analyze the rs1344706 SNP and identify common and rare variants in a targeted region of the ZNF804A gene in patients with SCZ, SAD, BPD compared with control group	ZNF804A gene (rs1344706)	Common variants were identified; rs3046266, rs1366842 and rs12477430
			A comparison of the three identified variants between SCZ, SAD and BPD did not show statistical differences
			There was significant difference in the allele frequency between patients and control; patients had significant higher frequency of (A) allele and lower frequency of (C) allele
			There was significant difference in genotype frequency between patients and control
			ZNF804A gene is involved in the etiology of SZC, SAD and BPD
Zhou et al 2021[17]	To explore the correlation between rs1344706 polymorphism of ZNF804a gene and the integrity of white matter in schizophrenic cases	ZNF804A gene (rs1344706)	The FA value of the right posterior radiocrown in the patient group was lower than that in the control group, and the difference was statistically significant.
		PCR genotyping	The FA value of the right lower frontal occipital tract and the right upper radiocrown in the G allele carrier group was lower than that in the A allele homozygous group
			The rs1344706 GG/AG genotype of the ZNF804a gene locus in SCZ patients suffered from abnormal structure in a specific region of the brain
			The rs1344706 single nucleotide polymorphism of the ZNF804a gene may affect the integrity of the white matter of the brain in SZ patients and may be involved in the pathophysiological mechanism of SCZ

Continued.

Author and publication year	Objective	Targeting gene	Results and main findings
De Castro-Catala et al 2017[18]	To investigate the association of two ZNF804A polymorphisms (rs1344706 and rs7597593) with the positive dimension of schizotypy and psychotic-like experiences in non-clinical subjects	ZNF804A polymorphisms (rs1344706 and rs7597593)	The association analyses between rs7597593 and positive schizotypy and positive psychotic-like experiences showed a significant association in the whole sample
		WSS to assess schizotype	These associations were driven by females; those carrying the C allele had higher scores in the positive dimension of both variables compared to TT allele homozygotes
			Regarding rs1344706, no association was observed with schizotypy or psychotic-like experiences, neither in the whole sample nor by sex
			The study supported the inclusion of *ZNF804* variability in studies of the vulnerability for the development of psychopathology in non-clinical samples and consideration of sex as a moderator of this association
Wang et al 2016[19]	To investigate the association between rs1344706 and SCZ in samples from Jiangsu province region	ZNF804A gene (rs1344706)	There is no significant between-group difference in allele frequency or genotype frequency distribution
			The basic case-control association test demonstrated no significant association between rs1344706 of ZNF804Aand schizophrenia in total subjects or stratified by sex
			The study did not support the association of rs1344706 with schizophrenia in Han Chinese
Mallas et al 2016[20]	To assess the impact of ZNF804A risk variant on FA in patients with SCZ, in those with BD and in healthy controls	ZNF804A gene (rs1344706)	Significant reductions in FA across a widely distributed brain network were positively associated both with a diagnosis of SCZ or BPD and with the double (homozygous) presence of the ZNF804A rs1344706 risk variant (A)
			The main effect of genotype was medium and the effect in the SCZ group alone was large with no significant effects in BPD or controls
			Homozygosis for risk allele A of SNP rs1344706 of ZNF804A confers risk for SZ and BD, and impaired functional connectivity
			This genetic variant promotes reduced WM integrity in a widespread network
Wei et al 2015[21]	To examine the effects of ZNF804A rs1344706 on brain GM more precisely and completely	ZNF804A gene (rs1344706)	The risk allele (T) in SCZ patients compared to the non-risk allele (G), was associated with thinner cortex in the bilateral precuneus, left precentral gyrus, and several other regions, associated with a smaller cortical surface area in the left superior parietal, precuneus cortex and left superior frontal, and associated with a lower cortical volume in the left superior frontal, left precentral, and right precuneus in SCZ patients
			In control, the T allele was associated with the increased cortical measurements compared to the G allele in the same regions as those mentioned above
			ZNF804A rs1344706 has significant effects on cortical thickness, surface area, and cortical volume in multiple regions of the brain cortex
			ZNF804A rs1344706 may aggravate the risk for schizophrenia by exerting its effects oncortical thickness, surface area, and cortical volume in these brain regions

BPD: Bipolar disorder, FA: fractional anisotropy; GM: gray matter, NREM: non-rapid eye movement, SAD: schizoaffective disorder, SCZ: schizophrenia, SNP: single nucleotide polymorphism, WM: white matter. WSS: Wisconsin schizotype scale

Data review and collection

Reviewing the data of included studies were done through revising the abstract of each study, then reviewing the whole article for more details. A specially designed excel sheet was used to extract the data of interest of each article, then revising data was done. Chosen data from eligible research articles were then transferred into one table to facilitate the comparison and summarizing of the data and other findings.

RESULTS

This review included six studies that met the eligible criteria.[16,21] The characteristics of the studies was summarized in Table 1, were two studies published in 2021, one study published in 2017, two studies published in 2016, and one study was published in 2015.[16-20] The six studies were conducted on four populations; three studies were conducted on the Chinese population, Mexican population, non-European population, and UK population.[16-21] There were two studies that included SCZ patients and other patients.[16,20] Only one study was conducted on one group of participants [18], whereas the remaining five studies were conducted on two groups; patient group and control healthy group.[16-21] The total number of all participants in all included studies was 4349; of them, there were 1861 (42.8%) schizophrenia patients; of them, one study reported that the number of SCZ, BPD, SAD patients were 395.

Regarding the objective and results of studies (Table 2), there were several objectives reported; however, they can be collective as studying the association or impact of ZNF804A variants on the white matter and gray matter between SCZ patients and the control group.[17,21] Also, the association between ZNF804A and SCZ was investigated, and the association between ZNF804A variants and the positive dimension of schizotypy and psychotic-like experience in non-clinical patients.[18,19] The other two studies included SCZ and patients with BPD, with the addition of SAD patients in one study.[16,20] These two studies investigated common and rare variants of the ZNF804A gene in SCZ, BPD, and SAD patients and the impact of ZNF804A risk variants on fractional anisotropy among SCZ and BPD patients.[16,20]

All studies investigated rs1344706 of ZNF804A, with additional restriction sites investigated by –studies; one study investigated rs3046266, rs1366842, rs12477430, and one study investigated rs7597593.[16,18] There were three studies reported using TaqMan SNP assay for SNP assessment, two studies reported using PCR genotyping, and one study didn't report the assay used.[16-21]

The results and main findings of studies varied due to variations in the objective of each study, so we tried to combine findings that discuss close objectives in order to obtain meaningful findings. The studies that included patients with SCZ and other patients (BPD, SAD patients) reported that there was significant variation in the allele frequency and genotype frequency between patients of SCZ, BPD, and SAD and the control group, where patients had a significantly higher frequency of A allele and lower frequency of C allele.[16] The other study showed that there was a considerable reduction in fractional anisotropy across a widely distributed network and were positively associated with the diagnosis of SCZ and BPD with the homozygous presence of A allele of rs1344706 in the ZNF804A gene.[20] ZNF804A gene variant (rs1344706) was involved in the etiology of SCZ, BPD, and SAD, and the homozygous A allele of rs1344706 in the ZNF804A gene grants risk for SCZ, BPD, and impaired functional connectivity; this genetic variant promoted reduced integrity of white matter in a widespread network.[16,20] The other study that investigated the integrity of white matter in SCZ patients showed that the fractional anisotropy value was lower in SCZ patients compared to the control group at the right posterior radio crown with significant variation. The fractional anisotropy value was lower in the C allele carriers compared to those with the homozygous A allele. SCZ patients with rs1344706 CC/AC suffered from an abnormal structure in a specific region of the brain. This SNP of ZNF804A was reported to affect the integrity of the white matter of the brain of SCZ patients and may be involved in the pathophysiology of the disease.[17]

The study concerned with the gray matter showed that SCZ patients with the A allele were associated with thinner cortex in the bilateral precuneus, smaller cortical surface area in the left superior parietal, and lower cortical volume in the left superior frontal compared to SCZ patients with C allele. The rs1344706 of the ZNF804A gene had a significant impact on the cortical thickness, surface area, and cortical volume in multiple regions of the brain cortex. This SNP carries the risk of SCZ by exerting its impact on the previous three regions.[21]

Of the remaining two studies, one study showed that the frequency of allele and genotype wasn't significant between the control group and the SCZ group. Moreover, it was reported that there was no association between rs1344706 of the ZNF804A gene and SCZ.[19] The last study showed a significant association between rs7597593 and positive schizotypy; the association was driven by females who carried the C allele compared to those carrying the T homozygous allele. On the other hand, there was no association between rs1344706 and schizotypy or psychotic-like experiences.[18]

DISCUSSION

Schizophrenia has multiple hypotheses for its etiology; one of them is the influence of the genetic components.[6] Based on a survey from Sweden of more than two million nuclear families, it was estimated that the genetic contribution was 64%.[22] Common and rare DNA gene variants may contribute to schizophrenia development.[23] The association between the ZNF804A gene variant at the rs1344706 has been reported in many studies.[7,8,12,13]

However, there is a lack of systematic analysis of these studies, one meta-analysis was published in 2014 and included articles published until 2013, but as far as we know, there was no systematic analysis or meta-analysis for this subject after that.[14] So, we conducted this systematic review to review articles published after this date, and we included six studies published between 2015 and 2021. Although the included studies in this review had a different aim, we could conclude the main findings of the studies.

The association between rs1344706 of the ZNF804A gene and SCZ was found in four studies out of the six studies, whereas the other two studies didn't find such association.[16-20] The association was concluded by the significant increase in the frequency of genotype and allele (A) among SCZ patients, as reported in one study.[16] This finding was also supported by another study, where it was found that the presence of homozygous A allele was associated with a reduction in fractional anisotropy, which in turn positively associated with the diagnosis of SCZ. Also, the genetic variant of ZNF804A enhanced the reduction of the white matter integrity in a widespread network.[20] Also, another study supported the previous finding, where it was found that this SNP (rs1344706 of ZNF804A gene) affected the integrity of white matter of the brain of SCZ patients and was suggested to be involved in the pathophysiology of the disease.[17] Also, it was found that this SNP under investigation affected the gray matter and had an impact on the cortical thickness, volume, and surface area. This SNP was found to be a risk factor for developing SCZ, and this risk can be explained by its impact on the previous three regions.[21]

On the other hand, there was no association found between ZNF804A (rs1344706) and SCZ in the Han Chinese population, whereas such association was found in another study conducted in the Chinese population.[19,21] Also, this SNP (rs1344706) was reported to have no association with schizotypy or psychotic-like experiences, whereas rs7597593 was positively associated with schizotypy among females and those carrying C allele contrasted with the findings regarding rs1344706 in the same study which was conducted among the non-European population.[18] This may drive a suggestion that the risk of rs1344706 for developing SCZ disease may be affected by other genetic factors that vary between different populations. Actually, our conclusion was in agreement with the report of the previous meta-analysis that found that the association between rs1344706 and SCZ was found in the Caucasian population and Asian population, but not in other populations.[14] Therefore, the ZNF804A gene variant (rs1344076) can't be used as a predictor for developing SCZ disease.

CONCLUSION

The rs1344706 of the ZNF804A gene was associated with the etiology of schizophrenia, with the A allele being the risk allele for developing the diseases; this was observed and concluded by the increased frequency of A allele among schizophrenia patients. Also, this gene variant was found to affect the integrity of white matter, affected the gray matter, and was associated with cortical volume, thickness, and surface area in multiple regions of the brain cortex. However, only two studies reported no association, and these two studies were conducted on a different population. So, the association of the ZNF804A gene variant with schizophrenia may be affected by other genetic factors that vary between different populations. Therefore, further studies should be conducted to investigate further factors that may affect the impact or the association of the ZNF804A gene variant with schizophrenia. Until the reveal of these factors and the determination of the association between this gene variant and the disease, ZNF804A at rs1344706 can't be used as a predictor for schizophrenia.

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