Boulenouar *et al.*
Egyptian Journal of Medical Human Genetics (2022) 23:81
https://doi.org/10.1186/s43042-022-00269-x

Egyptian Journal of Medical Human Genetics

REVIEW

Open Access

An actualized screening of schizophrenia-associated genes

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Abstract

Background: Schizophrenia is a psychotic disorder that impacts around 0.5% to 1.2% of the world's population. It has been well established that heredity plays an essential role in the causation of schizophrenia, with genetic heritability of up to 80%. A several new schizophrenia susceptibility genes were identified at the start of the twenty-first century. The aim of this systematic review will be to explore the association between single nucleotide polymorphisms (SNPs) and schizophrenia risk in people all over the world.

Methods: This systematic review collected available data on genetic variants associated with schizophrenia in worldwide populations. A PubMed and Science Direct search was investigated to identify all studies published until December 2020 on genetic susceptibility to schizophrenia in various populations, excluding family studies, transversal studies, cohort studies, experimental studies, and descriptive studies; those that demonstrate an association between repeat polymorphism (CNV, VNTR, etc.). All researches on genetic predispositions of schizophrenia and accepting the predetermined inclusion criteria were included in this systematic review.

Findings: Thirty-six studies focused on the schizophrenia-associated genes were retained in which a total of 44 polymorphisms among 26 susceptibility genes to schizophrenia have been associated in the world populations.

Conclusion: Despite the few number of studies published about genetic of schizophrenia, some genetic variations have been consistently correlated to schizophrenia, particularly in China, as this analysis shows. Further data, especially from genome-wide association studies, might contribute in the development of a reference for schizophrenia genetic susceptibility markers.

Keywords: Genetics, Schizophrenia, Systematic review, Genes, Polymorphisms, Psychiatry

Introduction

Schizophrenia is conceptualized as a psychotic disorder according to DSM-5. Delusions, hallucinations, and disordered speech are basic "positive symptoms" that may be reliably identified with schizophrenia and may be regarded crucial for a successful diagnosis [1]. With an early onset in late adolescence or early adulthood, the disease affects about 0.5% to 1.2% of the global population. The most common clinical manifestations are positive symptoms, particularly hallucinations and delusions, on the one hand, and negative symptoms, such as reduced mood, speech and interest, as well as language and behavioral disorders, on the other hand [2].

It has been well established that heredity plays a significant role in the causation of schizophrenia, with genetic heritability of up to 80% [3]. Evidence in this context is available from family studies, genetic associations, and genetic linkage studies. Despite the high heritability, the genetic susceptibility factors that contribute to this disease have not been fully elucidated [4].

The scientific community has long sought to understand the pathogenesis of schizophrenia; however, due to high disease's complexity, this objective has proven difficult to achieve. Researchers have browsed the entire

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human genome for loci and genetic alterations (e.g., single nucleotide polymorphisms [SNPs]) that may be related to schizophrenia and other psychiatric disorders over the last decade [5].

A number of new schizophrenia susceptibility genes were identified at the start of the twenty-first century, and to this day more than 1000 genes have been analyzed for their potential association with schizophrenia. These genes were discovered through association studies based on their chromosomal position or their function. Among the genes that have been suggested to converge functionally on schizophrenia risk, we highlight *ACE*, *GRM3*, *GSTs*, *DTNBP1*, *EFHD2*, *ERBB4*, *GABRB2*…[5].

A recent systematic review and meta-analysis indicated that *AMBRA1*, *ANK3*, *ARNTL*, *CDH13*, *EFHD1*, *MHC*, *PLXNA2*, and *UGT1A1* were revealed to be linked with SCZ or bipolar disorder (BD) diagnosis in at least two independent samples [6].

Similar to other psychiatric diseases, schizophrenia arises from an interplay between genetic and environmental factors. Studies in Chinese, Spanish, Indian, Iranian, Caucasian, and other populations around the world have shown robust genetic predispositions to this disease. This systematic review aims to collect available information on the genetic determinants of schizophrenia, more precisely to explore the association between single nucleotide polymorphisms (SNPs) and schizophrenia risk in people all over the world.

Methods used for systematic review

This systematic review was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This article will discuss the epidemiology and genetics of schizophrenia in the global population. This is a systematic review based on publicly available data. As a result, no ethical approval is needed.

Bibliographic search

We searched Medline through PubMed and Science Direct databases for all existing genome-wide associations studies (GWAS) of schizophrenia that has been published in English from database inception until December 2020. Additionally, the reference lists of pertinent articles and reviews were checked for further articles.

Selection of studies

We included observational studies, particularly cases–control studies that assessed the link between genetic polymorphisms and schizophrenia in various populations.

To focus on genetic as a complex trait of schizophrenia we excluded (1) family studies, transversal studies, cohort studies, experimental studies and descriptive studies; (2) those that demonstrate an association between repeat polymorphism (CNV, VNTR, etc.), mutations and schizophrenia.

For studies reported in several reports, we considered the most detailed reporting on the largest sample size. Three authors (H.B., F.G., and A.H.O.) individually examined articles for inclusion (titles, abstracts, and then full texts).

Data extraction, assessment, and synthesis

Three investigators (H.B., F.G., and A.H.O.) extracted data from qualified articles using an essentialist data extraction form. The gathered information contained the country of the study, study population, sample size, mean age, range and proportion of men for cases and controls, genotyping method, gene and polymorphism studied, and the outcome (effects of studied polymorphism on the disease).

Due to high heterogeneity among included studies, the impact of a genetic variant on schizophrenia (their association, or none association) was identified as linked (YES) or unlinked (NO) based on whether the polymorphism was associated or not with a risk of schizophrenia.

A fourth experienced investigator double-checked all collected evidence for consistency (Hm.B.).

Our decision to conduct a narrative synthesis of the collected data is informed by the small number of qualifying studies and the enormous variation between research pertaining to sample population characteristics and evaluation of the association of genetic polymorphisms and schizophrenia.

Results of the systematic review

Literature search

Our initial database search identified 5804 records from PubMed (n = 1632) and Science Direct (n = 4173); after removal of duplicates (n = 352), 5452 records remained. Since checking titles and abstracts, we identified 5220 records to be irrelevant and excluded them. We examined the complete texts of the remaining 232 articles to see if they were appropriate, of which 36 were eventually added [7–42] and 196 were excluded with reasons as indicated in Fig. 1.

Populations, genetic evaluation, and results

Of the 36 studies analyzed, 25 articles enrolled patients with schizophrenia of Asian origin (69,44%) [7–10, 12, 13, 15–20, 22–25, 28, 29, 33, 36–40, 42]. Patients of European ancestry were included in 6 articles (16,66%) [11, 26, 27, 30, 32, 41], whereas only 2 of African origin (5,55%)

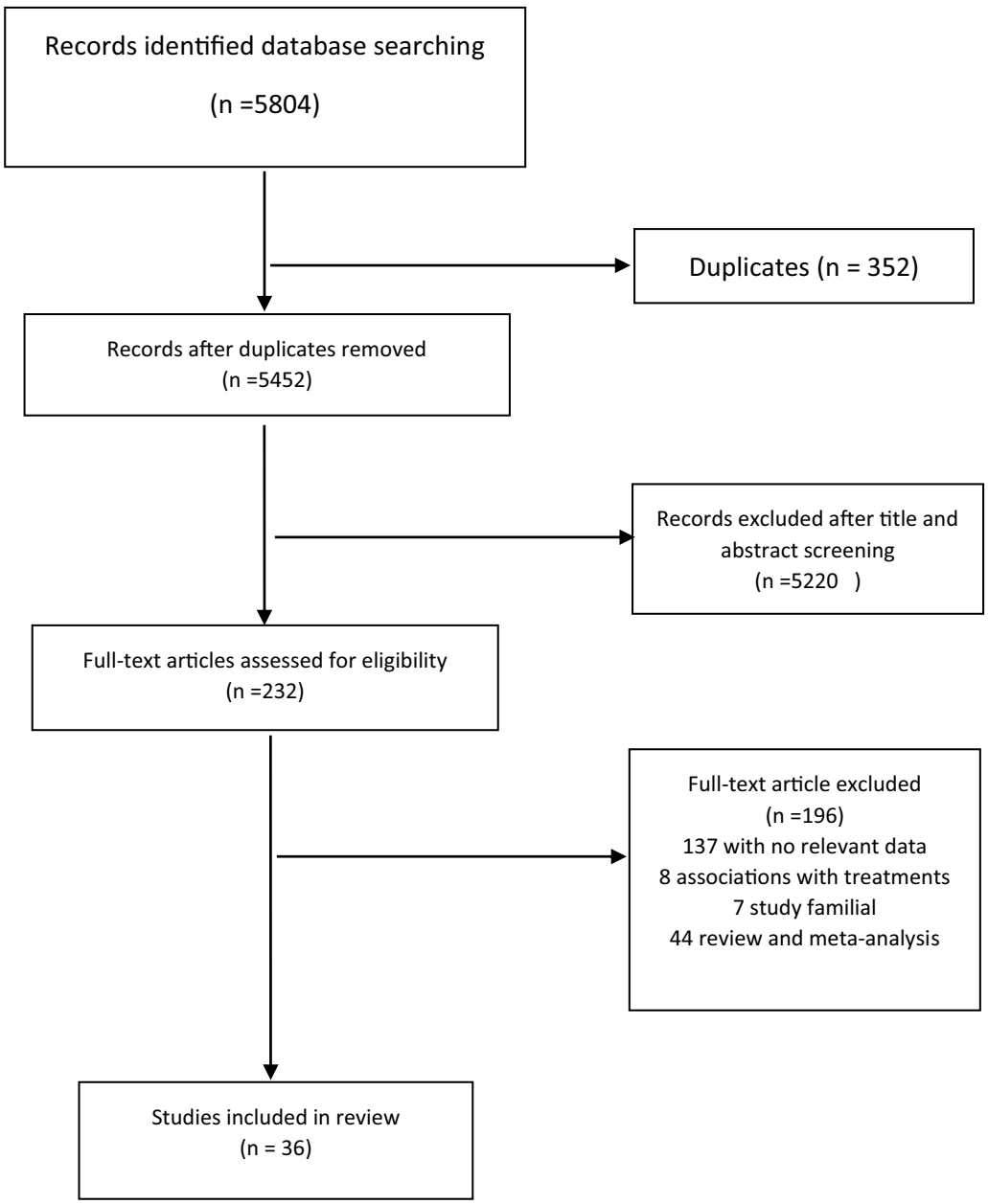

Fig. 1 Preferred reporting items for the systematic reviews and meta-analysis (PRISMA)

[21, 35], and the self-reported ethnic background in the last 3 article is African, African-American, Asian, and European [14, 31, 34]. All studies have been carried out on patients who had schizophrenia. Participants ranged in age from 16 to 76 years, with a men ratio ranging from 46 to 100% based on the population. Across studies, a total of 121 polymorphisms (including single nucleotide polymorphisms (SNPs) and insertion/deletions among 39 different genes were investigated (Table 1).

All SNPs in the selected studies fall in multifunctional scaffold proteins that are expressed in neurons and interact with multiple proteins involved in neuronal migration, glutamatergic, neurotransmission, signal transduction, and hippocampal development, all of which are implicated in the etiology of schizophrenia [15]. Indels were located primarily in the angiotensin converting enzyme (*ACE*), *NQO2*, and *PAI-1* genes. The aim of all of the researches was to see whether there was

Table 1 The different genes investigated within the selected articles

Gene	Polymorphisms	Country	Date
1. ACE I/D	I/D	Iran	2015
2. AUTS2	rs6943555	Turkey	2020
3. C3	rs11569562	China	2018
	rs344555		
	rs2241393		
	rs445750		
4. CACNA2D2	rs12496815	China	2020
	rs3806706		
	rs45536634		
5. DAO	rs3741775	Taiwan	2017
6. DAOA	rs3916956	Taiwan	2017
	rs2391191		
	rs778292		
	rs3918342		
	rs1421292		
7. DISC	rs1417584	Pakistan	2020
	rs1954175		
	rs821616		
	rs113012343		
8. DISC1	rs821616	China	2016
	rs821597		
9. DRD2	rs7116768	China	2018
	rs1799732		
10. DTNBP1	rs3213207	Korea	2009
	rs1011313		
	rs760761		
	rs2619522		
11. EFHD2	rs2473357	china	2020
	rs71631726		
	rs140124965		
	rs10927785		
12. ERBB4	rs839523 (G/A)	Jordan	2017
	rs3748962 (A/G)		
13. GABRB2	rs12187676 (G/C)	Iran	2020
	rs1816072 (T/C)		
14. GLRX5	rs1007814	China	2016
15. GRIA1	rs1428920	Korea	2012
	rs1552834		
	rs1422889		
	rs10035143		
	rs2926835		
16. GRIK4	rs79526501	China	2017
	rs4582985		
	rs11218016		
	rs6589847		
	rs56275759		
17. GRM3	rs187993	European &American	2005
	rs13242038		
	rs917071		
	rs6465084		
	rs2228595		
	rs1468412		
	rs3804100		
18.GSTs	GSTM1	Tunisia	2012
	GSTT1		
19. HDAC	HDAC3 (rs2530223)	Korea	2010
	HDAC4 (rs1063639)		
	HDAC10 (rs155048)		
20. HSPA1A	rs1008438	Poland	2018
	rs562047		
21. HSPA1B	rs6457452	Poland	2019
	rs2763979		
	rs539689		
	rs9281590		
22. HSPA1L	rs2075800	Poland	2018
23. IFNGR2	Q64R(Gln64Arg)	Tunisia	2016
24. MTHFR	C677T	USA	2006
25. NQO2	I/D	Japan	2003
26. NRG1	rs3924999	China	2016
27. NRXN1	rs10490168	China	2011
	rs2024513		
	rs10174398		
	rs10195460		
	rs13382584		
	rs1558852		
28. OPRM1	rs1799971	China	2013
	rs2075572		
	rs648893		
	rs671531		
29. PAI-1	4G/5G (I/D)	Turkey	2016
30. PDE4B	rs1354064	Caucasian	2008
	rs4320761	Africa, America	
	rs1040716		
	rs910694		
	rs1321177		
	rs2144719		
	rs783038		
	rs599381		
31.PPARα	αL162V	Croatia	2014
32. RANBP9	rs24023	Korea	2014
	rs442458		
	rs6940759		
	rs204226		
	rs11759518		
	I/D (rs16724)		
33. RELN	rs1062831	China	2019
	rs3808039		
	rs362746		

Table 1 (continued)

Gene	Polymorphisms	Country	Date
	rs736707		
34. SAT-1	-1415 T/C SNP	Spain	2009
35. TCF4	rs1261085	China	2020
	rs1261084		
	rs8766		
	rs9960767		
	rs2958182		
	rs12966547		
36. TLR2	rs3804099	Korea	2013
	rs3804100		
37. VEGFA	rs699947	China	2015
	rs25648		
	rs833070		
	rs3024997		
	rs10434		
38. VRK2	rs2312147	China	2015
	rs1051061		
	rs2043890		
	rs3732136		
39. XPC	Ala499Val	Iran	2019
	PAT		
	Lys939Gln		

a correlation between genetic determinants and schizophrenia in general populations.

Schizophrenia-associated genes

We identified 26 genes and 44 significant genetic polymorphisms implicated in schizophrenia in the research included in this review. Four studies about the 26 genes showing an association with schizophrenia were conducted in the Chinese population *DISC1* (rs821616, rs821597), *GLRX5* (rs1007814), *NRG1* (rs3924999), *TCF4* (rs2958182) [18, 20, 40]. Four other studies in Chinese Han population C3 (Complement 3) polymorphism (rs11569514), *CACNA2D2* (rs45536634), four polymorphisms of *NRXN1* (rs10490168, rs2 024513, rs13382584, rs1558852), and two polymorphisms of *OPRM1* (rs1799971. rs2075572) [13, 16, 37, 42]. In the Korean population, a similar associations were detected with *GRIA1* (rs1428920, rs2926835), *TLR2* (rs3804099, rs3804100), *HDAC3* (rs2530223) *HDAC4* (rs1063639), *DTNBP1* (rs760761, rs2619522) [23–25, 33]. Three other studies analyzed previously shown to be associated with schizophrenia in the northern and northeast Chinese han population *EFHD2* (rs2473357) [8, 10, 28]. Studies in Iranian population showed that the II genotype of the I/D polymorphism of *ACE* gene, (rs1816072 (T/C)) polymorphism of *GABRB2* and the (Haplotype Val-Lys) of *XPC* gene have a significant association with the susceptibility of schizophrenia [19, 29, 38].

It has already been found that there is a correlation between (GSTT1) polymorphism of *GSTs*, and Q64R (Gln64Arg) polymorphism of *IFNGR2* and the risk of this disease in the Tunisian population [21, 35]. Similar results were observed in Turkish with *AUTS2* (rs6943555) [32], Taiwanese with *DAOA* (rs778292, rs3918342, rs1421292) [12], Pakistanian with *DISC* (rs1417584) [15], Jordanian with *ERBB4* (rs839523) (G/A) [7], and Japanese population with *NQO2* (Deletion) [17] gene polymorphisms, respectively (Table 2).

One study conducted in mixed ethnic sample (Caucasian and African-American population) demonstrated an association between schizophrenia [14] and polymorphisms in *PDE4B* (rs1354064, rs4320761, rs1040716, rs910694, rs1321177, rs2144719, rs783038, rs599381) (Table 2).

Studies with lack of association

Twelve studies from various population did not find a significant association with schizophrenia [9, 11, 12, 22, 26, 27, 30, 31, 34, 36, 39] (Table 2).

Discussion

In this research, we used a systematic review to evaluate the correlation between polymorphisms and schizophrenia in the global population by integrating data from all qualifying studies. These powerful studies serve as informative summaries of the field's progress. Furthermore, a systematic review of smaller research will theoretically help entice and plan pathophysiological hypotheses for further genomic, transcriptomics, proteomics, and drug studies, particularly in unique populations. They can cover the research community's reflection on the diversity and discrepancies in samples, approaches, and conclusions through schizophrenia association, as well as make sense of current and prospective meta- and mega-analysis studies.

Our analysis showed that 75% of the overall pooled polymorphisms of these genes are SNPs (*AUTS2, C3, CACNA2D2, DAO, DAOA, DISC, DISC1, DRD2, DTNBP1, EFHD2, ERBB4, GABRB2, GRLX5, GRIA1, GRIK4, HDAC, HSPA1A, HSPA1B, HSPA1L, NRG1, NRXN1, OPRM1, PDE4B, RANBP9, RELN, SAT-1, TCF4, TLR2, VEGFA, VRK2*) and 25% of the others types of polymorphisms (*ACE, GRM3, GSTs, IFNGR2, MTHFR, NQO2, PAI-1, PPARα, XPC*).

After examining several articles across various populations, we selected 25 articles from the Asian population including 21 studies which found a significative association between polymorphism and schizophrenia, and four studies who failed to find an association. There are

Table 2 The genetic polymorphisms implicated in schizophrenia included in this review

References	Ethnicity	Total sample	No. of case/control	Mean age (case/control)	% Men (case/control)	Genotyping method	Gene	Polymorphism	Associated/no associated
Mazaheri and Saadat [29]	Iranian	726	363/363	41.4±13.1/39.7±11.1	73.8%/73.8%	PCR Assay	ACE	I/D	Yes (insertion with women)
Ozsoy et al. [32]	Turkish	252	100/152	39.11 ± 10.08/ 47.74 ± 13.26	55%/60.5%	PCR–RFLP	AUTS2	rs6943555	Yes
Zhang et al. [37]	Chinese Han	2240	1086/1154	34.24 ± 12.26/	/	Mass ARRAY/	C3	rs11569562	Yes (rs11569514)
				36.47 ± 10.93		PCR	I	rs344555	
							I	rs2241393	
			I				rs11569514		
							I	rs445750	
Fu et al. [16]	Chinese Han	1536	761/775	34.61 ± 12.02/	58.2%/56.2%	MALDI-TOF–MS technology	CACNA2D2	rs12496815	Yes (rs45536634)
				34.74 ± 11.41			I	rs3806706	
							I	rs45536634	
Chu et al. [12]	Taiwan	515	248/267	39.22 ± 10.64/	56%/81.6%	SNPlex genotyping system	DAO	rs3741775	No
				36.13 ± 11.95					
Chu et al. [12]	Taiwan	515	248/267	39.22 ± 10.64/	56%/81.6%	SNPlex genotyping system	DAOA	rs3916956	Yes (rs778292, rs3918342, rs1421292)
				36.13 ± 11.95			I	rs2391191	
							I	rs778292	
							I	rs3918342	
							I	rs1421292	
Fatima et al. [15]	Pakistani	300	150/150	34.07 ± 9.5/	65.3%/61.3%	PCR/PCR–RFLP	DISC	rs1417584	Yes (rs1417584)
				33.8 ± 10.6			I	rs1954175	
							I	rs821616	
							I	rs113012343	
He et al. [18]	Chinese	484	248/236	54.39 ± 13.39/	64.5%/65.6%	MassARRAY	DISC1	rs821616	Yes (rs821616,
				56.11 ± 12.91			I	rs821597	rs821597)
Zhang et al. [39]	Northeast Chinese Han	630	306/324	44.6 ± 7.3/	50.3%/48.5%	PCR	DRD2	rs7116768	No
				45.3 ± 15.9			I	rs1799732	
Pae et al. [33]	Korean	1509	908/601	38.9 /33.7	50.5%/50.9%	Pyrosequencer	DTNBP1	rs3213207	Yes (rs760761, rs2619522)
							I	rs1011313	
							I	rs760761	
							I	rs2619522	
Gao et al. [28]	Northern Chinese	602	281/321	41.1 ± 7.1/	50.8%/48.2%	PCR	EFHD2	rs2473357	Yes (rs2473357)
	Han			43.7 ± 7.4			I	rs71631726	
							I	rs140124965	
							I	rs10927785	
Al-Eitan et al. [7]	Jordan	380	185/195	45 .9 ± 12.6/	100%/100%	PCR	ERBB4	rs839523 (G/A)	Yes (rs839523)
				31.4 ± 8.1			I	rs3748962 (A/G)	
Heidari Nia et al. [19]	Iranian	390	190/200	36.48 ±10.52/ 36.40±10.88	/	Tetra-ARMS-PCR	GABRB2	rs12187676(G/C)	Yes (rs1816072)
							I	rs1816072 (T/C)	
Yang et al. [40]	Chinese	1504	893/611	50.4 ± 13.4/	56.4%/54.5%	PCR	GLRX5	rs1007814	Yes (rs1007814)
				42.0 ± 9.9					
Kang et al. [23]	Korean	598	218/380	42.2 ± 10.6/	/	PCR	GRIA1	rs1428920	Yes (rs1428920,

Table 2 (continued)

References	Ethnicity	Total sample	No. of case/control	Mean age (case/control)	% Men (case/control)	Genotyping method	Gene	Polymorphism	Associated/no associated
				44.3 ± 6.3			I	rs1552834	rs2926835)
							I	rs1422889	
							I	rs10035143	
							I	rs2926835	
Ren et al. [36]	Chinese	2068	1034/1034	45.06 ± 12.88/	60.4%/56.8%	MassARRAY	GRIK4 rs79526501	No	
				34.06 ± 10.0		Sequenom	I	rs4582985	
							I	rs11218016	
							I	rs6589847	
							I	rs56275759	
Norton et al. [31]	European & American	1390	674/716	44.5 ± 14.6/	71.5%/63.6%	Sequenom	GRM3	rs187993	No
				41.5 ± 11.5		MassARRAY	I	rs13242038	
						PCR	I	rs917071	
							I	rs6465084	
							I	rs2228595	
							I	rs1468412	
							I	rs3804100	
Raffa et al. [35]	Tunisian	261	138/123	32.67 ± 7.44/	86.9%/80.4%	PCR	GSTs	GSTM1	Yes (GSTT1)
				31.28 ± 5.28			I	GSTT1	
Kim et al. [25]	Korean	512	278/234	42.91 ± 10.91/	67.9%/41%	SeqMan II software	HDAC	HDAC3 (rs2530223)	Yes (HDAC3, HDAC4)
				36.06 ± 6.08			I	HDAC4 (rs1063639)	
							I	HDAC10 (rs155048)	
Kowalczyk et al. [26]	Polish	1080	401/679	41.3 ± 12.4/	59.6%/52.8%	PCR–RFLP	HSPA1A	rs1008438	No
				40.4 ± 8.7		TaqMan	I	rs562047	
Kowalczyk et al. [27]	Polish	901	377/524	41.1 ± 12.3/	59.4%/55.34	PCR–RFLP/ TaqMan Assays	HSPA1B	rs6457452	No
				39.8 ± 9.1			I	rs2763979	
							I	rs539689	
							I	rs9281590	
Kowalczyk et al. [26]	Polish	1080	401/679	41.3 ± 12.4/	59.6%/52.8%	PCR–RFLP	HSPA1L	rs2075800	No
				40.4 ± 8.7		TaqMan			
Jemli et al. [21]	Tunisian	391	225/166	39.7 ± 10.02/	77.7%/61.4%	PCR–RFLP	IFNGR2	Q64R(Gln64Arg)	Yes (Men)
				28.37 ± 8.44					
Philibert et al. [34]	European, African-American, Hispanic, Asian	565	206/359	39.8 ± 10.8/	63.5%/50.6%	Flurescent Primer	MTHFR	C677T	No
						Probe			
Harada et al. [17]	Japanese	336	102/234	46.9 ± 14.2/	59.8%/70.1%	PCR	NQO2	I/D	Yes (Deletion)
				46.4 ± 9.1					
He et al. [18]	Chinese	484	248/236	54.39 ± 13.39/	64.5%/65.6%	MassARRAY	NRG1 rs3924999	Yes (rs3924999)	

Table 2 (continued)

References	Ethnicity	Total sample	No. of case/control	Mean age (case/control)	% Men (case/control)	Genotyping method	Gene	Polymorphism	Associated/no associated
				56.11 ± 12.91					
Yue et al. [42]	Chinese Han	1506	768/738	33.5 ± 8.7/	46.8%/48.5%	TaqMan	NRXN1	rs10490168	Yes (rs10490168, rs2024513, rs13382584,
				32.2 ± 6.4			I	rs2024513	rs1558852)
							I	rs10174398	
							I	rs10195460	
							I	rs13382584	
							I	rs1558852	
Ding et al. [13]	Chinese Han	528	264/264	37.44 ± 11.04/	58.3%/55.3%	PCR–RFLP	OPRM1	rs1799971	Yes (rs1799971
				36.38 ± 12.27			I	rs2075572	rs2075572)
							I	rs648893	
							I	rs671531	
Yenilmez et al. [41]	Turkish	250	150/100	/	/	PCR	PAI-1	4G/5G (I/D)	No
Fatemi et al. [14]	Caucasian, African	1482	878/604	/	/	TaqMan	PDE4B	rs1354064	Yes (rs1354064,
	American						I	rs4320761	rs4320761, rs1040716, rs910694, rs1321177, rs2144719, rs783038, rs599381
							I	rs1040716	
							I	rs910694	
							I	rs1321177	
							I	rs2144719	
							I	rs783038	
							I	rs599381	
Nadalin et al. [30]	Croatian	394	203/191	40.1 ± 8.8/	54.6%/45.5%	PCR–RFLP	PPARα	L162V	No
Bae et al. [9]	Korean	842	449/393	44.92/54.62	55.7%/56.5%	TaqMan Assay	RANBP9	rs24023	No
							I	rs442458	
							I	rs6940759	
							I	rs204226	
							I	rs11759518	
							I	Ins/Supp(rs16724)	
Bai et al. [10]	Northeast Chinese Han	1536	761/775	34.61 ± 12.02/	58.2%/56.1	Mass ARRAY	RELN	rs1062831	Yes (rs362746)
				34.74 ± 11.41			I	rs3808039	
							I	rs362746	
							I	rs736707	
Bermudo-Soriano et al. [11]	Spanish	593	180/413	41.95/38.85	53.8%/38%	PCR	SAT-1	-1415 T/C SNP	No
Gao et al. [20]	Chinese	1076	448/628	36.1 ± 10.2/	49.5%/42.9	PCR/SNPscan	TCF4	rs1261085	Yes (rs2958182)
				35.7 ± 9.7			I	rs1261084	
							I	rs8766	
							I	rs9960767	
							I	rs2958182	
							I	rs12966547	

Table 2 (continued)

References	Ethnicity	Total sample	No. of case/control	Mean age (case/control)	% Men (case/control)	Genotyping method	Gene	Polymorphism	Associated/no associated
Kang et al. [24]	Korean	591	286/305	42.8 ± 10.8/	66.7%/48.1%	PCR	TLR2	rs3804099 (Asn199Asn)	Yes (rs380499,
				36.6/6.8			I	rs3804100 (Ser450Ser)	Rs3804100)
Gao et al. [22]	Chinese Han	1986	1034/952	49.44 ± 17.95/	64.7%/51.2%	TaqMan	VEGFA	rs699947	No
				34.45 ± 10.12			I	rs25648	
							I	rs833070	
							I. rs3024997	rs3024997	
							I	rs10434	
Zhang et al. [8]	Northwest	893	360/533	37.2 ± 10.4/	49.1%/43.5%	PCR	VRK2	rs2312147	Yes (rs3732136)
	Chinese Han			35.6 ± 11.2			I	rs1051061	
							I	rs2043890	
							I	rs3732136	
Taghipour et al. [38]	Iran	721	361/360	41.9 ± 13.5/40.6 ± 13.2/	72.3%/74.1	SNP Alyze (TM) software	XPC	Ala499Val	Yes (Haplotype Val-Lys)
							I	PAT	
							I	Lys939Gln	

also 11 other studies from Europe, Africa, and the USA (2 African, 6 European, and 3 mixed African-American-European) among which 5 have found a relation between polymorphism and schizophrenia.

The Iranian study [29] investigated the role of the genotypes of I/D *ACE* polymorphism by PCR method. The deletion allele (D) was seen as a 191 bp band, whereas the insertion allele (I) was identified as a 478 bp band [29]. When compared to the DD genotype, the II genotype substantially reduced the risk of schizophrenia in females [29]. There was a strong linear relationship between the number of I alleles and the risk of schizophrenia in females. The sexes and the II genotype had a strong interaction [29]. The association between the ACE I/D polymorphism and the risk of schizophrenia has already been established. Two recent studies found contradictory results: the I allele was shown to be a protective factor in a Turkish population [43], although the D allele was found to be protective against schizophrenia and bipolar disorder in a Spanish population [44].

The study of *C3* polymorphisms is still a major field in schizophrenia research. Association between the SNP rs11569514 in *C3* and schizophrenia was investigated in Han Chinese population [37]. Interestingly, in the codominant model (TT vs. AA) the authors found a significant risk effect for rs11569514 on schizophrenia. Recent findings in the Tunisian population, as well as in the Brazilian population, show a significantly higher level of C3 protein in schizophrenia patients [45, 46].

In the research of Zhang et al. [39] among the northern Chinese Han population, there was no significant association between the (rs7116768) and (rs1799732) polymorphisms of the dopamine D2 receptor (*DRD2*) gene promoter region and schizophrenia [39], these results are consistent with those of previous research in a Spanish population [47], but are in contrast to the results in Brazilian population who found a significant association [48]. However, there are still some uncertainties concerning these associations.

The *GRM3* gene was not associated with schizophrenia in the European and American populations [31]. Similar results were observed in the Japanese population [49]. However, other studies have instead reported a link between *GRM3* genetic variation and risk of schizophrenia [50, 51].

Among single population studies, 12 variants of *NQO2* gene were identified in Japanese population [17] including the insertion/deletion (I/D) polymorphism of the 29 base pair nucleotide sequence in the promoter region. In the schizophrenia group, the frequency of the D allele was significantly higher than in the healthy controls. The current findings show that individuals with the deletion of the 29 bp sequence in the promoter region of the *NQO2* gene might be vulnerable to a specific type of schizophrenia [17]. Further research is needed on the implication of this polymorphism on schizophrenia.

One of the most promising potential genes for schizophrenia is neuregulin 1 (*NRG1*); the rs3924999 G/G genotype was associated with schizophrenia in the early onset subgroup (25 years) in the Chinese population [18]. Similar findings have been reported in Han Chinese and

Japanese populations, where the *NRG1* gene appears to contribute to schizophrenia susceptibility [52, 53].

In this research [14], 27 single nucleotide polymorphisms (SNPs) across the *PDE4B* gene were genotyped; several of these SNPs genotyped in the Caucasian population were substantially associated with schizophrenia. Two related intronic SNPs, rs1321177 and rs2144719, were particularly correlated to schizophrenia [14].

Although a number of studies have shown an association between the phosphodiesterase 4B (*PDE4B*) gene and the risk of schizophrenia, the findings are still inconclusive [54].

Reelin (RELN) is a protein involved in brain development and function and has been related to a variety of neuropsychiatric disorders. Bai et al. reported that the rs362746 of the *RELN* gene was associated with schizophrenia under the recessive and codominant models, in the Chinese population [10]. In Australia and Turkey, there was also a high correlation between this polymorphism and schizophrenia [55, 56].

The transcription factor 4 (*TCF4*) gene is highly expressed and plays a critical role in nervous system development, and it has long been implicated in the risk of developing schizophrenia [57].

The rs2958182 on *TCF4* gene showed a significant association with schizophrenia in a meta-analysis in Chinese population [20]. This conclusion is in agreement with previous studies, in different ethnicities like Malaysians population, and Han Chinese population [57, 58].

VRK2 is a serine/threonine protein kinase enzyme encoded by the *VRK2* gene on human chromosome 2p16.1. The *VRK2* rs3732136 polymorphism was shown to be substantially linked with schizophrenia in the study of Zhang et al. [8] in a Northwest Chinese Han population, similar results were reported in other genotype and haplotype association studies. The results suggest that the *VRK2* gene may play an important role in the development of schizophrenia in the Han population of northwest China [8]. The polymorphisms of serine/threonine-protein kinase (*VRK2*) were correlated to schizophrenia in two recent studies performed in Northern European and Asian populations [59, 60].

Several other polymorphisms were genotyped in different populations; for example, *AUTS2* (rs6943555) [32], *CACNA2D2* (rs45536634) [16], *DAOA* (rs778292, rs3918342, rs1421292) [12], *DISC* (rs1417584) [15], *DISC1* (rs821616) [18], *DNTBP1* (rs3213207, rs1011313, rs760761, and rs2619522) [33], *EFHD2* (rs2473357) [28], *ERBB4* (rs839523) [7], *GABRB2* (rs12187676) [19], *GLRX5* (rs1007814) [40], *GRIA1* (rs1428920, rs2926835) [23], *GSTs* (GSTT1) [35], *HDAC* (rs1063639) [25], *IFNGR2* (Q64R) [21], *NRXN1* (rs10490168, rs2024513, rs13382584, rs1558852) [42], *OPRM1* (rs1799971, rs2075572) [13], *TLR2* (rs3804099) [24] and *XPC* [38] each found a significant association with schizophrenia.

In contrast some studies which genotyped other polymorphisms in several genes, for example, *DAO* [12], *GRIK4* [36], *HSPA1A* [26] *HSPA1B* [27], *HSPA1L* [26], *MTHFR* [34], *PAI-1* [41], *PPARα* [30], *RANBP9* [9], *SAT-1* [11], *VEGFA* [22], found no significant association with schizophrenia.

To fully understand the correlation between these polymorphisms and schizophrenia, further research with larger populations and prospective approaches is needed. Therefore, this systematic review still reveals new data of the impact of genes in schizophrenia risk.

A rigorous and systematic literature review, as well as the inclusion of multiple potential genetic risk factors for schizophrenia, is among the review's strengths. As many sample sizes were small, it is possible that the sample sizes were insufficient to detect a true association, especially because schizophrenia is most likely polygenic and influenced by many variants with small effect sizes.

Conclusion

Despite the few number of studies published about genetic of schizophrenia, some genetic variations have been consistently correlated to schizophrenia, particularly in China, as this analysis shows. Further data, especially from genome-wide association studies, might contribute in the development of a reference for schizophrenia genetic susceptibility markers.

Abbreviations

ACE: Polymorphism in angiotensin-converting enzyme; AMBRA1: Autophagy and beclin 1 regulator 1; ANK3: Ankyrin 13; ARNTL: Aryl hydrocarbon receptor nuclear translocator-like; AUTS2: Autism susceptibility gene 2 protein; BD: Bipolar disorder; C3: Complement 3; CACNA2D2: Calcium voltage-gated auxiliary subunit alpha 2 delta 2; CDH13: Cadherin-13; DAO: D-amino acid oxidase.; DAOA: D-amino acid oxidase activation.; DISC: Disrupted in schizophrenia; DISC1: Disrupted in schizophrenia 1; DNA: Deoxyribonucleic acid; DRD2: Dopamine receptor D2; DSM 5: Diagnostic and statistical manual of fifth edition; DTNBP1: Dystrobrevin-binding protein 1; EFHD1: EF-hand domain family member D1; EFHD2: EF-hand domain family member D2; ERBB4: Erb-b2 receptor tyrosine kinase 4; GABRB2: Gamma-aminobutyric acid type A receptor subunit beta 2; GLRX5: Glutaredoxin 5; GRIA1: Glutamate ionotropic receptor AMPA type subunit 1; GRIK4: Glutamate ionotropic kainite receptor 4; GRM3: Glutamate metabotropic receptor 3; GSTS: The glutathione S-transferase; GWAS: Genome-wide association study; HDACHDAC3: Histone deacetylase 3; HSPA1A: Heat shock protein family A (Hsp70) member 1A; HSPA1B: Heat shock protein family A (Hsp70) member 1B; HSPA1L: Heat shock protein family A (Hsp70) member 1-like; IFNGR2: Interferon gamma receptor 2; Indel: Insertion/deletion; MHC: The major histocompatibility complex; MTHFR: Methylenetetrahydrofolate reductase; NQO2: N-Ribosyldihydronicotinamide:quinone reductase 2; NRG1: Neuregulin 1; NRXN1: Neurexin 1; OPRM1: μ-Opioid receptor gene; OR: Odds ratio; P: P value; PAI-1: Plasminogen activator inhibitor-1; PDE4B: Phosphodiesterase 4B; PLXNA2: Plexin A2; PPARα: Peroxisome proliferator activated receptor alpha; PRISMA: Preferred reporting items for the systematic reviews and meta-analysis; PubMed: Journal database; RANBP9: Ran-binding protein 9; RELN: Reelin is a protein coding gene; SAT-1: Spermidine/spermine N-1 acetyltransférase; SCZ: Schizophrenia; SNPs: Single

nucleotide polymorphisms; TCF4: Transcription factor 4; TLR2: Toll-like receptor 2; UGT1A1: UDP glucuronosyltransferase family 1 member A1; VEGFA: Vascular endothelial growth factor A; VNTR: Variable number tandem repeat; VRK2: Vaccinia-related kinase 2; XPC: Xeroderma pigmentosum, complementation group C.

Acknowledgements
Not applicable.

Authors' contributions
HB and AR designed research; FG, HB and AHO conducted the bibliographic research and selected the studies involved in this systematic review under the supervision of HB and AR; FG, HB and AHO performed the data extraction, assessment, and synthesis; FG, HB and AHO wrote the paper under the supervision of HB and AR; HB and AR had primary responsibility for final content. All authors read and approved the final manuscript.

Funding
No funding was received for the present systematic review.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 10 September 2021 Accepted: 16 February 2022
Published online: 16 April 2022

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