Investigating the association between common DRD2/ANKK1 genetic polymorphisms and schizophrenia: a meta-analysis

Journal of Genetics (2021)100:59
https://doi.org/10.1007/s12041-021-01306-1

RESEARCH ARTICLE

Investigating the association between common *DRD2/ANKK1* genetic polymorphisms and schizophrenia: a meta-analysis

PARHAM HABIBZADEH[1], AZIM NEMATI[2], HASSAN DASTSOOZ[1,3], AFSANEH TAGHIPOUR-SHESHDEH[1], PRISHO MARIAM PAUL[4], ALI SAHRAIAN[5] and MOHAMMAD ALI FAGHIHI[1,6]*

[1]*Persian BayanGene Research and Training Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[2]*Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran*
[3]*Italian Institute for Genomic Medicine (IIGM), University of Turin, Turin, Italy*
[4]*Department of Biotechnology, CMS College Kottayam, Kottayam, India*
[5]*Research Center for Psychiatry and Behavioral Sciences, Shiraz University of Medical Sciences, Shiraz, Iran*
[6]*Center for Therapeutic Innovation, Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, USA*
*For correspondence. E-mail: MFaghihi@med.miami.edu.

Received 30 June 2020; revised 18 November 2020; accepted 29 March 2021

Abstract. Genetic factors play an important role in the pathogenesis of schizophrenia. Dysregulations in the dopaminergic system have long been known to play an influential role in the development of this disorder. Although a large number of studies have investigated the association between genetic polymorphisms in the genes involved in this system and the risk of schizophrenia, the results have been inconsistent. In this meta-analysis, we searched for publications in Ovid Medline, Embase, Web of Science (science citation index expanded), and PsycNET for articles published until January 2020. We identified case–control studies investigating the association between four common genetic polymorphisms (rs6277, rs1799732, rs1800497, and rs1801028) and the risk of schizophrenia. The studies were subsequently selected according to the predefined inclusion and exclusion criteria. The data extraction was conducted according to the PRISMA guidelines. We also assessed the quality of the studies and investigated publication bias using funnel plot and Egger's regression test. The association analysis was conducted in allelic, dominant, and recessive genetic models. Subsequently, bioinformatics analysis of the effect of the polymorphisms found to be significantly associated with schizophrenia on protein stability, posttranslational modifications, and 3D protein structure was conducted. This meta-analysis showed that Taq1A (allelic model: OR, 0.856, 95% CI, 0.734–0.998) has a protective effect against the development of schizophrenia. Further, it was found that this variant may decrease ANKK1 protein stability. Further, this polymorphism was found to lead to the gain of modifications sites for ubiquitination (Ubi. score = −1.894) and methylation (Meth. score = −0.834). Several genetic factors contribute to the susceptibility of schizophrenia. The updated knowledge emerging from this meta-analysis showing the protective effect of rs1800497 polymorphism (Taq1A) can shed light on the role of Taq1A polymorphism in the susceptibility to schizophrenia and also pave way for further functional studies investigating the role of ANKK1 protein in the pathogenesis of schizophrenia.

Keywords. schizophrenia; polymorphism; single nucleotide; genetic variation; meta-analysis.

Introduction

Schizophrenia is a common psychiatric disorder with an average lifetime prevalence of about 1% (Kahn *et al.* 2015). As pointed out by a plethora of investigations (e.g. twin studies), this disorder is highly heritable (Cardno and Gottesman 2000). Notwithstanding the elusive aetiologic basis of this disorder, for quite some time, dysregulations in dopaminergic neurotransmission have been hypothesized to have an instrumental role in the pathogenesis of schizophrenia (van Rossum 1966). One of the most studied markers for the development of schizophrenia has been the

Parham Habibzadeh and Azim Nemati contributed equally to this work.

Supplementary Information: The online version contains supplementary material available at https://doi.org/10.1007/s12041-021-01306-1.

Published online: 12 August 2021

Table 1. Characteristics of the studied SNPs (data extracted from the NCBI database).

SNP	Chromosome (GRCh38)	Chromosome (GRCh37)	Canonical SPDI
rs6277	11:113412737	11:113283459	NC_000011.10:113412736:G:A
rs1799732	11:113475529	11:113346252	NC_000011.10:113475529:G:GG
rs1800497	11:113400106	11:113270828	NC_000011.10:113400105:G:A
rs1801028	11:113412762	11:113283484	NC_000011.10:113412761:G:C

SDPI, sequence position deletion insertion.

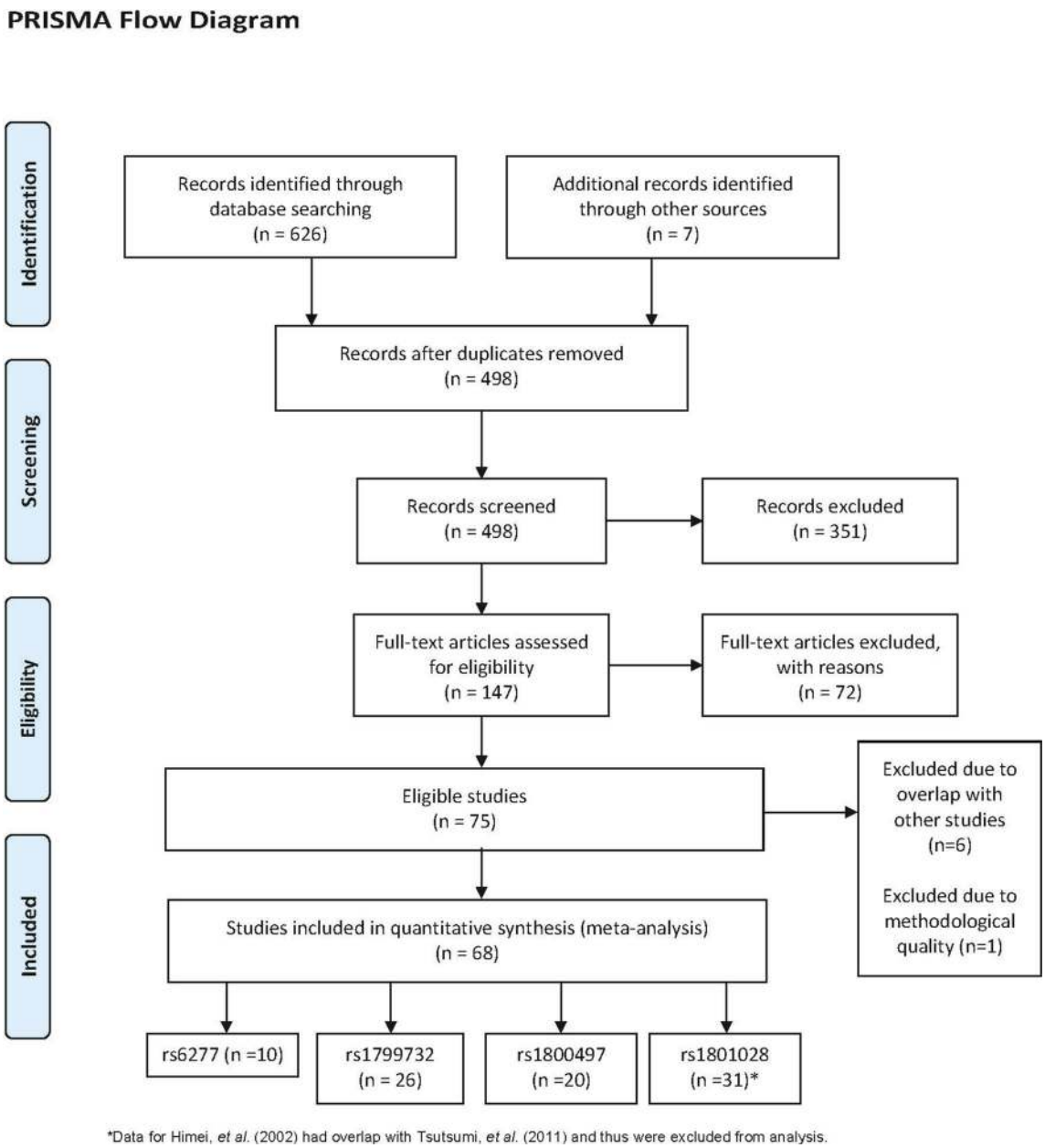

Figure 1. Flowchart of the study identification process.

DRD2 gene, located on chromosome 11q22.2, coding for dopamine receptor D2 (Seeman 1987). Further, the elevated striatal DRD2 density has been demonstrated in patients with schizophrenia (Abi-Dargham *et al.* 2000). The association of DRD2, the target of all affective antipsychotic medications, with schizophrenia has also been corroborated by a

Table 2. The baseline characteristics of the included studies.

Author	Year of Publication	Country of origin	Ethnicity	Source of control population	Cases (*n*)	Control (*n*)	Male cases (*n*)	Male controls (*n*)	Mean age cases	Mean age controls	Diagnostic criteria	NOS score
Comings *et al.*	1991	USA	Caucasian	Hospital-based	87	69	–	–	–	–	DSM-III	4
Sanders *et al.*	1993	USA	Caucasian	Population-based	55	51	50	48	44	60	DSM-III-R and RDC	5
Campion *et al.*	1994	France	Caucasian	Population-based	80	80	–	–	–	–	DSM-III	5
Gejman *et al.*	1994	USA	Caucasian	Hospital-based	106	113	–	–	–	–	DSM-III-R	4
Asherson *et al.*	1994	UK	Caucasian	Hospital-based	112	64	–	–	–	–	DSM-III-R	5
Nothen *et al.*	1994	Germany	Caucasian	Population-based	179	138	–	–	–	–	-	5
Hattori *et al.*	1994	Japan	East Asian	Population-based	100	100	50	50	–	–	DSM-III-R	5
Laurent *et al.*	1994	France	Caucasian	–	113	184	79	110	42	49	DSM-III	4
Sobell *et al.*	1994	USA	Caucasian	–	338	1914	–	–	–	–	–	4
Arinami *et al.*	1996	Japan	East Asian	Hospital-based	136	279	166	–	44.9	49.2	DSM-III-R or ICD-10	5
Chen *et al.*	1996	China	East Asian	Population-based	114	88	57	35	40	27.5	DSM-III-R	6
Crawford *et al.*	1996	USA	Caucasian	Hospital-based	84	81	–	–	–	–	DSM-III-R	6
Dollfus *et al.*	1996	France	Caucasian	Population-based	62	161	–	–	–	–	DSM-III-R and 11 other diagnostic classifications	6
Jonsson *et al.*	1996	Sweden	Caucasian	–	104	67	75	45	45.8	38.7	DSM-III-R	6
Ohara *et al.*	1996	Japan	East Asian	Population-based	153	121	77	51	46.3	34.4	DSM-IV	6
Sasaki *et al.*	1996	USA, Canada, Italy	Caucasian	Hospital-based	273	255	182	88	32	36	DSM-III-R	5
Arinami *et al.*	1997	Japan	East Asian	Hospital-based	260	312	151	173	44.4	48.7	DSM-III-R	6
Harano *et al.*	1997	Japan	East Asian	Hospital-based	70	101	46	46	47	67	DSM-III-R	6
Fujiwara *et al.*	1997	Japan	East Asian	–	52	26	–	–	–	–	DSM-III-R and ICD-10	5
Kaneshima *et al.*	1997	Japan	East Asian	Population-based	78	112	35	36	36.3	23	RDC and DSM-IV	7
Li *et al.*	1998	UK	Caucasian	Hospital-based	151	145	145	–	29.48	–	DSM-III-R Or DSM-IV	6
Spurlock *et al.*	1998	Europe	Caucasian	Population-based	373	413	220	215	–	–	DSM-III-R	6
Ohara *et al.*	1998	Japan	East Asian	Population-based	170	121	89	51	43.5	35.4	DSM-IV	7
Stober *et al.*	1998	Germany	Caucasian	Population-based	260	290	157	159	–	29.3	ICD-10	7
Breen *et al.*	1999	UK	Caucasian	Population-based	439	437	–	–	–	–	DSM-III or DSM-IIIR or DSM-IV	7
Inada *et al.*	1999	Japan	East Asian	Population-based	234	94	130	47	54	46	DSM-III-R	7
Tallerico *et al.*	1999	Canada	Caucasian	–	50	51	–	–	–	–	DSM-III-R	5
Jonsson *et al.*	1999	Sweden	Caucasian	–	129	179	82	86	44.6	45.3	DSM-III-R	6
Serretti *et al.*	2000	Italy	Caucasian	Hospital-based	366	267	161	128	–	46.62	DSM-IV	6
Dubertret *et al.*	2001	France	Caucasian	Population-based	50	50	37	39	–	–	DSM-IV	6
Hori *et al.*	2001	Japan	East Asian	Population-based	241	201	124	100	52.7	54.78	DSM-IV	7
Himei *et al.*	2002	Japan	East Asian	Population-based	190	103	120	53	53.1	33.1	DSM-IV	7
Morimoto *et al.*	2002	Japan	East Asian	–	48	48	22	–	25.1	–	ICD-10	6
Jonsson *et al.*	2003	Sweden	Caucasian	–	173	236	109	148	44	39.8	DSM-III-R	7
Kampman *et al.*	2003	Finland	Caucasian	Population-based	93	94	–	–	–	–	DSM-IV	7
Dubertret *et al.*	2004	France	Caucasian	Population-based	103	83	81	67	–	–	DSM-IV	6

Table 2. (contd)

Author	Year of Publication	Country of origin	Ethnicity	Source of control population	Cases (*n*)	Control (*n*)	Male cases (*n*)	Male controls (*n*)	Mean age cases	Mean age controls	Diagnostic criteria	NOS score
Lawford *et al.*	2005	Australia	Caucasian	Population-based	154	148	133	105	36.2	36.8	DSM-IV	7
Hanninen *et al.*	2006	Finland	Caucasian	Population-based	188	384	103	206	43.1	44.4	DSM-IV	8
Hoenicka *et al.*	2006	Spain	Caucasian	Population-based	131	364	76	–	–	–	DSM-IV	7
Kukreti *et al.*	2006	India	Indian	Population-based	101	145	56	–	–	–	DSM-IV	7
Parsons *et al.*	2007	Spain	Caucasian	Population-based	119	165	78	81	41.2	26.89	DSM-IV	7
Vijayan *et al.*	2007	India	Indian	Population-based	213	196	81	–	34.4	–	DSM-IV	8
Behravan *et al.*	2008	Iran	Caucasian	–	38	63	17	24	42	46	DSM-IV	7
Lafuente *et al.*	2008	Spain	Caucasian	Hospital-based	243	291	132	112	34.05	61.7	DSM-IV	7
Monakhov *et al.*	2008	Russia	Caucasian	Population-based	311	364	163	138	35.3	31.7	DSM-IV	7
Sanders *et al.*	2008	Europe	Caucasian	Population-based	1870	2002	–	–	–	–	DSM-IV	8
Luu *et al.*	2008	China	East Asian	–	211	201	112	90	43	42	DSM-IV	6
Betcheva *et al.*	2009	Bulgaria	Caucasian	Population-based	255	556	124	289	45.3	50.5	DSM-IV	8
Cordeiro *et al.*	2009	Brazil	Mixed	Population-based	229	733	148	496	27.2	31.8	DSM-IV	8
Gupta *et al.*	2009	India	Indian	Population-based	254	225	155	139	29.22	31.08	DSM-IV	8
Srivastava *et al.*	2009	India	Indian	Hospital-based	233	224	112	130	29.34	34.63	DSM-IV	7
Dubertret *et al.*	2010	France	Caucasian	Population-based	144	142	–	–	–	73.6	DSM-IV	8
Fan *et al.*	2010	China	East Asian	Population-based	421	404	–	–	30.74	28.15	DSM-IV	8
Saiz *et al.*	2010	Spain	Caucasian	Population-based	288	421	172	216	36.3	40.6	DSM-IV	9
Kurt *et al.*	2010	Turkey	Caucasian	Population-based	73	60	40	25	38.11	36.51	DSM-IV	8
Tsutsumi *et al.*	2011	Japan	East Asian	Population-based	407	384	221	194	47.2	42.1	DSM-IV-TR	8
Watanabe *et al.*	2012	Japan	East Asian	Population-based	648	664	348	337	39.8	38.4	DSM-IV	8
Xiao *et al.*	2013	China	East Asian	Population-based	120	100	65	55	44.6	45.3	DSM-IV-TR	8
Cordeiro *et al.*	2014	Brazil	Mixed	Population-based	235	834	–	–	–	–	DSM-IV	8
Zhang *et al.*	2014	China	East Asian	Population-based	396	399	260	224	31	31	DSM-IV	9
Arab *et al.*	2015	Egypt	African Arab	Population-based	120	100	72	–	32.6	–	DSM-IV	8
Han *et al.*	2017	China	East Asian	Population-based	690	430	398	231	27.2	26.9	CCMD-3	8
Alfimova *et al.*	2019	Russia	Caucasian	Population-based	389	238	136	90	32.07	30.32	ICD-10	8
Kaur *et al.*	2019	India	Indian	Population-based	443	150	–	–	–	–	ICD-10	7
Zhang *et al.*	2019	China	East Asian	Population-based	306	324	154	157	44.6	45.3	DSM-IV	8
Funahashi *et al.*	2019	Japan	East Asian	Population-based	100	100	48	49	58.7	58.6	DSM-V	8
Nunes *et al.*	2019	Brazil	Mixed	Population-based	144	72	36	64	–	–	–	5
Poorshekar *et al.*	2019	Iran	Caucasian	Population-based	100	100	63	62	37.94	37.94	–	6

Table 3. rs6277 genotype and allele frequency distribution.

	Cases (*n*)			Controls (*n*)			Cases (%)		Controls (%)		PHWE	
Reference	C/C	C/T	T/T	C/C	C/T	T/T	C	T	C	T	Cases	Control
Lawford *et al.* (2005)	48	75	31	27	70	51	55.51948	44.48052	41.89189189	58.10810811	0.862481	0.728738
Hanninen *et al.* (2006)	59	92	37	104	176	104	55.85106	44.14894	50	50	0.91605	0.10247
Hoenicka *et al.* (2006)	30	61	40	46	174	144	46.18321	53.81679	36.53846154	63.46153846	0.469154	0.557312
Kukreti *et al.* (2006)	41	38	22	48	64	33	59.40594	40.59406	55.17241379	44.82758621	0.027094	0.194704
Monakhov *et al.* (2008)	99	152	60	78	183	103	56.2701	43.7299	46.56593407	53.43406593	0.903279	0.844807
Betcheva *et al.* (2009)	58	128	66	192	253	111	48.4127	51.5873	57.28417266	42.71582734	0.788511	0.097893
Gupta *et al.* (2009)	104	112	38	76	120	29	62.99213	37.00787	60.44444444	39.55555556	0.38721	0.083629
Fan *et al.* (2010)	366	52	3	368	34	1	93.11164	6.888361	95.53349876	4.466501241	0.446254	0.818987
Tsutsumi *et al.* (2011)	367	38	1	341	43	2	80.51471	19.48529	86.63366337	13.36633663	0.070923	0.340652
Han *et al.* (2017)	554	109	27	410	13	7	88.18841	11.81159	96.86046512	3.139534884	2.16E-10	1.84E-25

genomewide association study, identifying *DRD2* as one of the major risk genes for schizophrenia (Beaulieu and Gainetdinov 2011; Schizophrenia Working Group of the Psychiatric Genomics 2014). Ankyrin repeat and kinase domain containing 1 (*ANKK1)* is another gene that is closely associated with *DRD2* and is closely related to dopaminergic signalling (Koeneke *et al.* 2020). Taq1A, a polymorphism originally associated with *DRD2* has recently been found to be located on the *ANKK1* gene (Neville *et al.* 2004).

Association between schizophrenia and the four common single-nucleotide polymorphisms, namely rs6277, rs1799732, rs1800497 and rs1801028 (table 1), which are associated with *DRD2* has been extensively studied (Dollfus *et al.* 1996; Breen *et al.* 1999; Jonsson *et al.* 2003). Unfortunately, due to different genetic backgrounds, potential confounding bias, and small sample size, the results of these investigations have been either conflicting or inconsistent. A meta-analysis including 10 case–control studies conducted by Glatt *et. al.* in 2004 to assess the potential association between rs1799732 polymorphism and schizophrenia failed to show any associations (Glatt *et al.* 2004). Other meta-analyses have also been performed in recent years to evaluate the association between *DRD2* polymorphisms and schizophrenia with inconsistent results (Glatt and Jonsson 2006; Watanabe *et al.* 2015; Yao *et al.* 2015; Wang *et al.* 2016). New genetic association studies which have not been included in these meta-analyses have been recently conducted to shed light on the association between different *DRD2* polymorphisms and schizophrenia (Kaur *et al.* 2019b; Zhang *et al.* 2019a). We have conducted this meta-analysis to provide a comprehensive assessment of the association between four common genetic polymorphism and schizophrenia.

Materials and methods

Search strategy and selection criteria

Potentially relevant literature published before January 2020 were retrieved from Ovid Medline, Embase, Web of Science (science citation index expanded), and PsycNET using the combination of following terms: ('DRD2' OR 'Dopamine receptor 2' OR 'Dopamine receptor D2' OR 'Dopamine D2 receptor') AND ('SNP' OR 'polymorphism' OR 'variant' OR 'genotype' OR 'allele') AND ('Schizophrenia'). The reference lists of all retrieved articles were also reviewed for other eligible articles. The search strategy was not confined to any language or time period.

Studies were considered eligible to test the research hypothesis of this meta-analysis if they met the following criteria: (i) case–control studies investigating the association between the mentioned polymorphisms (rs6277, rs1799732, rs1800497, and rs1801028) and schizophrenia; (ii) provide adequate data on genotype and/or allelic frequency of the studied variants in both cases (i.e., patients diagnosed with schizophrenia) and controls to calculate the odds ratio (OR) and 95% confidence interval (CI). Studies were excluded in case of one of the following conditions (i) not relevant to the mentioned genetic variants and schizophrenia; (ii) case reports and case series; (iii) book chapters, reviews, conference abstracts, comments, letters to the editor, animal studies and studies lacking a control group. In the case of repeated inclusion of subjects in more than one publication, we only included the study with the largest sample size.

Data extraction and quality assessment

Two investigators (AN and AT) independently reviewed all abstracts to evaluate the appropriateness of the articles and the eligibility criteria. Disagreements were resolved by a consensus and discussion with a third investigator (PH). The following information was extracted from the eligible studies: the first author's name, year of publication, country of origin, the ethnicity of the studied population, gender (male percentage), source of control population, mean age of cases and controls, diagnostic criteria, number of genotyped cases and controls, genotype/allele frequency for cases and controls. Study authors were contacted to identify further study and also the missing information. Newcastle–Ottawa scale (NOS) was used to assess the methodological quality of the included

Table 4. rs1799732 genotype and allele frequency distribution.

	Cases (*n*)			Controls (*n*)			Cases (%)		Controls (%)		PHWE	
References	Ins/Ins	Ins/Del	Del/Del	Ins/Ins	Ins/Del	Del/Del	Ins	Del	Ins	Del	Cases	Control
Arinami *et al.* (1997)	190	66	4	193	102	17	85.76923	14.23077	78.20513	21.79487	0.520258	0.469118
Li *et al.* (1998)	112	39	0	118	26	1	87.08609	12.91391	90.34483	9.655172	0.068424	0.737736
Ohera *et al.* (1998)	136	34	0	84	36	1	90	10	84.29752	15.70248	0.147418	0.173126
Stober *et al.* (1998)	207	50	3	236	53	1	89.23077	10.76923	90.51724	9.482759	0.992078	0.271373
Breen *et al.* (1999)	318	111	10	345	87	5	85.07973	14.92027	88.9016	11.0984	0.931919	0.852793
Inada *et al.* (1999)	156	72	6	51	40	3	82.05128	17.94872	75.53191	24.46809	0.494667	0.142519
Tallerico *et al.* (1999)	40	10	0	43	7	1	90	10	91.17647	8.823529	0.432058	0.293968
Jonsson *et al.* (1999)	114	15	0	142	34	3	94.18605	5.813953	88.82682	11.17318	0.483241	0.564348
Hori *et al.* (2001)	162	71	8	142	54	5	81.95021	18.04979	84.0796	15.9204	0.948493	0.960274
Himei *et al.* (2002)	118	69	3	71	27	5	80.26316	19.73684	82.03883	17.96117	0.043838	0.262065
Kampman *et al.* (2003)	86	7	0	88	6	0	96.23656	3.763441	96.80851	3.191489	0.70608	0.749251
Dubertret *et al.* (2004)	83	19	1	43	33	7	89.80583	10.19417	71.68675	28.31325	0.939612	0.851407
Parsons *et al.* (2007)	88	20	0	135	18	0	90.74074	9.259259	94.11765	5.882353	0.288945	0.439474
Lafuente *et al.* (2008)	208	33	2	235	54	2	92.38683	7.613169	90.03436	9.965636	0.589515	0.560906
Sanders *et al.* (2008)	1495	354	21	1643	341	18	89.41176	10.58824	90.58442	9.415584	0.993121	0.947429
Luu *et al.* (2008)	165	44	2	163	34	4	88.62559	11.37441	89.55224	10.44776	0.618177	0.17336
Cordeiro *et al.* (2009)	183	38	8	498	206	29	88.20961	11.79039	81.99181	18.00819	0.00221	0.190838
Gupta *et al.* (2009)	205	44	3	169	50	4	90.07937	9.920635	86.99552	13.00448	0.714035	0.892319
Srivastava *et al.* (2009)	161	65	7	172	48	4	83.04721	16.95279	87.5	12.5	0.887637	0.76003
Dubertret *et al.* (2010)	104	37	3	120	21	1	85.06944	14.93056	91.90141	8.098592	0.890378	0.938291
Saiz *et al.* (2010)	181	76	15	301	98	5	80.51471	19.48529	86.63366	13.36634	0.070923	0.340652
Kurt *et al.* (2010)	45	26	2	34	25	1	79.45205	20.54795	77.5	22.5	0.437847	0.131433
Xiao *et al.* (2013)	96	22	2	68	28	4	89.16667	10.83333	82	18	0.576065	0.606619
Zhang *et al.* (2014)	257	34	15	275	44	5	89.54248	10.45752	91.66667	8.333333	1.12E-12	0.0455
Funahashi *et al.* (2019)	74	25	1	69	29	2	86.5	13.5	83.5	16.5	0.481217	0.599996
Nunes *et al.* (2019)	9	36	99	9	23	40	18.75	81.25	28.47222	71.52778	0.031252	0.067179

studies (Stang 2010). Only studies with moderate or high methodological quality were included in the meta-analysis.

Statistical analysis

Chi-square goodness of fit test was used to determine deviation from Hardy–Weinberg equilibrium (HWE) in the studied populations. Cochran's Q test and the I^2 statistics were used to assess heterogeneity among included studies (Huedo-Medina *et al.* 2006). In case of I^2 values > 50% or Q statistic *P*-value < 0.1, random-effects model (Dersimonian-Laird method) was used. Otherwise, fixed-effects model was applied.

Pooled ORs with 95% CIs adopting dominant, recessive, and allelic models were used to estimate the strength of association between the genetic polymorphisms and schizophrenia. Subgroup analysis by ethnicity (Caucasian and East Asian) was also performed in the allelic model. Publication bias was assessed by visual inspection of the funnel plot and Egger's regression test (Begg and Mazumdar 1994; Egger *et al.* 1997). Statistical analysis was conducted using metaphor package in R software (v. 3.6.3) (see methods in electronic supplementary material at http://www.ias.ac.in/jgenet/) (Viechtbauer 2010).

Bioinformatics analysis

The effect of genetic polymorphisms found to be significantly associated with schizophrenia on protein stability was evaluated using the I-Mutant Suite tool (http://gpcr2.biocomp.unibo.it/cgi/predictors/I-Mutant3.0/I-Mutant3.0.cgi). Further, their effects on posttranslational modifications were investigated using AWESOME (http://www.awesome-hust.com) (Yang *et al.* 2019). The effect of SNP on protein structure was visualized using HOPE (https://www3.cmbi.umcn.nl/hope/) (Venselaar *et al.* 2010). Further, the 3D protein structure modelling was conducted using SWISSMODEL (https://swissmodel.expasy.org/) and energy minimization was carried out using SPDBV. Subsequently root-mean-square deviation (RMSD) value was calculated by PyMOL to evaluate the structural change in the protein as a result of the variant.

This meta-analysis was conducted in adherence to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline (Liberati *et al.* 2009).

Results

Study characteristics

The flow diagram depicting the study selection process is shown in figure 1. A total of 633 articles were initially identified through database search. This number was reduced to 498 after the removal of duplicates. Further, after assessing the articles based on the inclusion and exclusion criteria, 75 studies were found to be eligible (Comings *et al.* 1991; Itokawa *et al.* 1993; Sanders *et al.* 1993; Arinami

Table 5. rs1800497 genotype and allele frequency distribution.

	Cases (*n*)			Controls (*n*)			Cases (%)		Controls (%)		PHWE	
References	C/C	C/T	T/T	C/C	C/T	T/T	C	T	C	T	Cases	Control
Comings *et al.* (1991)	58	27	2	59	10	0	82.18391	17.81609	92.75362	7.246377	0.577131	0.516367
Sanders *et al.* (1993)	38	16	1	36	12	3	83.63636	16.36364	82.35294	17.64706	0.641393	0.173744
Campion *et al.* (1994)	60	19	1	58	20	2	86.875	13.125	85	15	0.710814	0.860783
Dollfus *et al.* (1996)	41	19	2	111	45	5	81.45161	18.54839	82.91925	17.08075	0.910937	0.866198
Jonsson *et al.* (1996)	70	30	4	45	18	4	81.73077	18.26923	80.59701	19.40299	0.728365	0.248359
Dubertret *et al.* (2001)	36	13	1	26	21	3	85	15	73	27	0.889728	0.643512
Dubertret *et al.* (2004)	71	29	3	30	40	13	83.00971	16.99029	60.24096	39.75904	0.985118	0.955967
Parsons *et al.* (2007)	92	24	3	93	68	4	87.39496	12.60504	76.9697	23.0303	0.355984	0.036911
Vijayan *et al.* (2007)	102	93	17	88	77	29	70.04717	29.95283	65.20619	34.79381	0.508453	0.080989
Behravan *et al.* (2008)	11	21	6	21	39	3	56.57895	43.42105	64.28571	35.71429	0.441939	0.005721
Lafuente *et al.* (2008)	157	81	5	184	90	13	81.27572	18.72428	79.79094	20.20906	0.137914	0.639709
Monakhov *et al.* (2008)	189	104	18	238	116	10	77.49196	22.50804	81.31868	18.68132	0.465598	0.350971
Srivastava *et al.* (2009)	123	93	17	107	96	21	72.74678	27.25322	69.19643	30.80357	0.919514	0.936423
Dubertret*et al.* (2010)	94	44	6	79	54	9	80.55556	19.44444	74.64789	25.35211	0.767561	0.955175
Cordeiro *et al.* (2014)	94	112	29	289	407	138	63.82979	36.17021	59.05276	40.94724	0.622044	0.792741
Zhang *et al.* (2014)	150	181	65	161	187	51	60.73232	39.26768	63.78446	36.21554	0.406561	0.772921
Arab *et al.* (2015)	77	43	0	55	33	12	82.08333	17.91667	71.5	28.5	0.016799	0.057062
Alfimova *et al.* (2019)	148	79	10	150	64	11	79.11392	20.88608	80.88889	19.11111	0.894106	0.230199
Kaur *et al.* (2019a, b)	202	205	36	63	72	15	68.73589	31.26411	66	34	0.106499	0.394532
Nunes *et al.* (2019)	75	61	8	35	29	8	73.26389	26.73611	68.75	31.25	0.329219	0.595141

et al. 1994; Asherson *et al.* 1994; Campion *et al.* 1994; Gejman *et al.* 1994; Hattori *et al.* 1994; Laurent *et al.* 1994; Nanko *et al.* 1994; Nothen *et al.* 1994; Shaikh *et al.* 1994; Sobell *et al.* 1994; Arinami *et al.* 1996; Chen *et al.* 1996; Crawford *et al.* 1996; Dollfus *et al.* 1996; Jonsson *et al.* 1996; Ohara *et al.* 1996; Sasaki *et al.* 1996; Tanaka *et al.* 1996; Arinami *et al.* 1997; Fujiwara *et al.* 1997; Harano 1997; Kaneshima *et al.* 1997; Verga *et al.* 1997; Li *et al.* 1998; Ohara *et al.* 1998; Spurlock *et al.* 1998; Stober *et al.* 1998; Breen *et al.* 1999; Inada *et al.* 1999; Jonsson *et al.* 1999; Tallerico *et al.* 1999; Serretti *et al.* 2000; Dubertret *et al.* 2001, 2004, 2010; Hori *et al.* 2001; Himei *et al.* 2002; Morimoto *et al.* 2002; Jonsson *et al.* 2003; Kampman *et al.* 2003; Lawford *et al.* 2005; Hanninen *et al.* 2006; Hoenicka *et al.* 2006; Kukreti *et al.* 2006; Parsons *et al.* 2007; Vijayan *et al.* 2007; Lafuente *et al.* 2008; Behravan *et al.* 2008; Luu *et al.* 2008; Monakhov *et al.* 2008; Sanders *et al.* 2008; Betcheva *et al.* 2009; Cordeiro *et al.* 2009; Gupta *et al.* 2009; Fan *et al.* 2010; Saiz *et al.* 2010; Srivastava *et al.* 2010; Kurt *et al.* 2011; Tsutsumi *et al.* 2011; Watanabe *et al.* 2012; Xiao *et al.* 2013; Alfimova *et al.* 2014; Cordeiro and Vallada 2014; Zhang *et al.* 2014; Arab and Elhawary 2015; Han *et al.* 2017; Alfimova *et al.* 2019; Funahashi *et al.* 2019; Kaur *et al.* 2019a; Nunes 2019; Poorshekar *et al.* 2019; Zhang *et al.* 2019b). However, after further investigations, six articles were not included in the meta-analysis due to the overlap of their studied populations with other published studies (Itokawa *et al.* 1993; Arinami *et al.* 1994; Nanko *et al.* 1994; Tanaka *et al.* 1996; Verga *et al.* 1997; Alfimova *et al.* 2014). The data for rs1801028 SNP presented in a study by Himei *et al.* (2002) was not included in the meta-analysis for this variant since it was already included in an investigation conducted by Tsutsumi *et al.* (2011). Further, one study was excluded because of low NOS score (Shaikh *et al.* 1994). At the end, 68 studies with 15,200 cases and 18,111 controls investigating the association of four genetic polymorphisms and schizophrenia were included in the meta-analysis. There were 31 studies with 8639 cases and 9743 controls investigated the association between rs1801028 and schizophrenia. The relationship between rs1800497 and schizophrenia was assessed in 20 studies involving 3416 cases and 3780 controls. For rs1799732 polymorphism, 26 studies with 6625 cases and 7139 controls were carried out to elucidate the relationship between this variant and schizophrenia. Ten studies involving 2908 cases and 3405 controls investigated the correlation between rs6277 variant and schizophrenia. Overall, the included studies represented different populations, namely Caucasian, East Asian, Indian, African Arab and mixed. The characteristics of the included studies are displayed in table 2. The distribution of the genotypes and allele frequencies for the studied SNPs across the included studies are demonstrated in tables 3–6.

Quantitative synthesis

***Analysis of association between rs6277 and schizophrenia*:** No significant association was observed between this polymorphism and schizophrenia under the studied genetic models: allelic model (OR, 0.998, 95% CI, 0.737–1.352), dominant model (OR, 1.131, 95% CI, 0.824–1.552), and recessive

Table 6. rs1801028 genotype and allele frequency distribution.

	Cases (*n*)			Controls (*n*)			Cases (%)		Controls (%)		PHWE	
References	C/C	C/G	G/G	C/C	C/G	G/G	C	G	C	G	Cases	Control
Gejman *et al.* (1994)	103	3	0	109	4	0	98.58491	1.415094	98.23009	1.769912	0.882513	0.848107
Asherson *et al.* (1994)	110	2	0	63	1	0	99.10714	0.892857	99.21875	0.78125	0.924043	0.949773
Nothen *et al.* (1994)	175	4	0	133	5	0	98.88268	1.117318	98.18841	1.811594	0.879837	0.828411
Hattori *et al.* (1994)	93	7	0	93	6	1	96.5	3.5	96	4	0.716833	0.028706
Laurent *et al.* (1994)	108	8	0	181	3	0	96.55172	3.448276	99.18478	0.815217	0.700493	0.911228
Sobell *et al.* (1994)	326	12	0	1848	65	1	98.22485	1.775148	98.24974	1.750261	0.739697	0.582425
Arinami *et al.* (1996)	124	12	0	265	14	0	95.58824	4.411765	97.49104	2.508961	0.59041	0.667294
Chen *et al.* (1996)	110	4	0	83	5	0	98.24561	1.754386	97.15909	2.840909	0.84879	0.783859
Crawford *et al.* (1996)	78	5	1	78	3	0	95.83333	4.166667	98.14815	1.851852	0.019597	0.865159
Ohara *et al.* (1996)	152	1	0	118	3	0	99.6732	0.326797	98.76033	1.239669	0.967651	0.890181
Sasaki *et al.* (1996)	261	12	0	245	9	1	97.8022	2.197802	97.84314	2.156863	0.710416	0.008913
Harano *et al.* (1997)	62	8	0	93	8	0	94.28571	5.714286	96.0396	3.960396	0.612108	0.678561
Fujiwara *et al.* (1997)	50	2	0	25	1	0	98.07692	1.923077	98.07692	1.923077	0.887559	0.92036
Kaneshima *et al.* (1997)	74	4	0	105	7	0	97.4359	2.564103	96.875	3.125	0.816216	0.732812
Spurlock *et al.* (1998)	359	14	0	396	17	0	98.12332	1.876676	97.94189	2.058111	0.711846	0.669345
Serretti *et al.* (2000)	329	37	0	252	15	0	94.94536	5.054645	97.19101	2.808989	0.308444	0.636742
Hori *et al.* (2001)	217	23	1	185	15	1	94.81328	5.186722	95.77114	4.228856	0.645064	0.264608
Morimoto *et al.* (2002)	42	6	0	42	6	0	93.75	6.25	93.75	6.25	0.644167	0.644167
Jonsson *et al.* (2003)	160	12	1	232	4	0	95.95376	4.046243	99.15254	0.847458	0.160443	0.895537
Dubertret *et al.* (2004)	97	6	0	80	3	0	97.08738	2.912621	98.19277	1.807229	0.760772	0.866838
Vijayan *et al.* (2007)	169	38	3	159	32	4	89.52381	10.47619	89.74359	10.25641	0.608971	0.12949
Sanders *et al.* (2008)	1796	73	1	1895	105	2	97.99465	2.005348	97.27772	2.722278	0.770417	0.662992
Gupta *et al.* (2009)	208	42	4	186	37	2	90.15748	9.84252	90.88889	9.111111	0.276386	0.915228
Srivastava *et al.* (2009)	200	32	1	189	34	1	92.70386	7.296137	91.96429	8.035714	0.815925	0.686484
Dubertret *et al.* (2010)	139	5	0	137	5	0	98.26389	1.736111	98.23944	1.760563	0.832096	0.830894
Fan *et al.* (2010)	387	32	1	377	26	0	95.95238	4.047619	96.77419	3.225806	0.695154	0.503392
Tsutsumi *et al.* (2011)	390	14	8	354	23	7	96.35922	3.640777	95.18229	4.817708	1.22E-25	1.06E-11
Watanabe *et al.* (2012)	607	40	1	617	46	1	96.75926	3.240741	96.38554	3.614458	0.689013	0.882635
Han *et al.* (2017)	632	51	7	396	26	8	95.28986	4.710145	95.11628	4.883721	3.5E-06	4.47E-13
Kaur *et al.* (2019a, b)	443	0	0	150	0	0	100	0	100	0	NA	NA
Poorshekar *et al.* (2019)	96	4	0	100	0	0	98	2	100	0	0.83829	NA

model (OR, 1.036, 95% CI, 0.681–1.575) (figure 2; table 7). Further, subgroup analysis in East Asian (OR, 0.575, 95% CI, 0.225–1.470) and Caucasian populations (OR, 1.265, 95% CI, 0.904–1.770) showed no significant associations.

***Analysis of the association between rs1799732 and schizophrenia*:** Summary results of the meta-analysis showed no significant association between rs1799732 and schizophrenia under allelic (OR, 0.966, 95% CI, 0.822–1.135), dominant (OR, 0.952, 95% CI, 0.800–1.133), and recessive models (OR, 1.060, 95% CI, 0.744–1.511) (figure 3; table 7). In addition, subgroup analysis in East Asian (OR, 0.845, 95% CI, 0.672–1.062) and Caucasian populations (OR, 1.060, 95% CI, 0.837–1.342) demonstrated no significant associations.

***Analysis of association between rs1800497 and schizophrenia*:** The pooled results showed that rs1800497 polymorphism was significantly associated with schizophrenia in the studied populations under the allelic genetic model (OR, 0.856, 95% CI, 0.734–0.998) (figure 4). However, no significant associations were observed under other genetic models: dominant model (OR, 0.861, 95% CI, 0.723–1.026), and recessive model (OR, 0.755, 95% CI, 0.555–1.025) (figure 4; table 7). Subgroup analysis in East Asian (OR, 1.139, 95% CI, 0.930–1.395) and Caucasian populations (OR, 0.873, 95% CI, 0.671–1.135).

***Analysis of the association between rs1801028 and schizophrenia*:** This meta-analysis failed to find any significant associations between rs1801028 and schizophrenia under different genetic models: allelic model (OR, 1.009, 95% CI, 0.893–1.140), dominant model (OR, 1.020, 95% CI, 0.897–1.160), and recessive model (OR, 0.994, 95% CI, 0.402–2.456) (figure 5; table 7). The subgroup analysis in East Asian (OR, 0.995, 95% CI, 0.824–1.201) and Caucasian populations (OR, 1.292, 95% CI, 0.906–1.842) was also unable to detect any significant associations.

Evaluation of heterogeneity and publication bias

There was significant heterogeneity across the included studies for rs6277, rs1799732, and rs1800497 under all

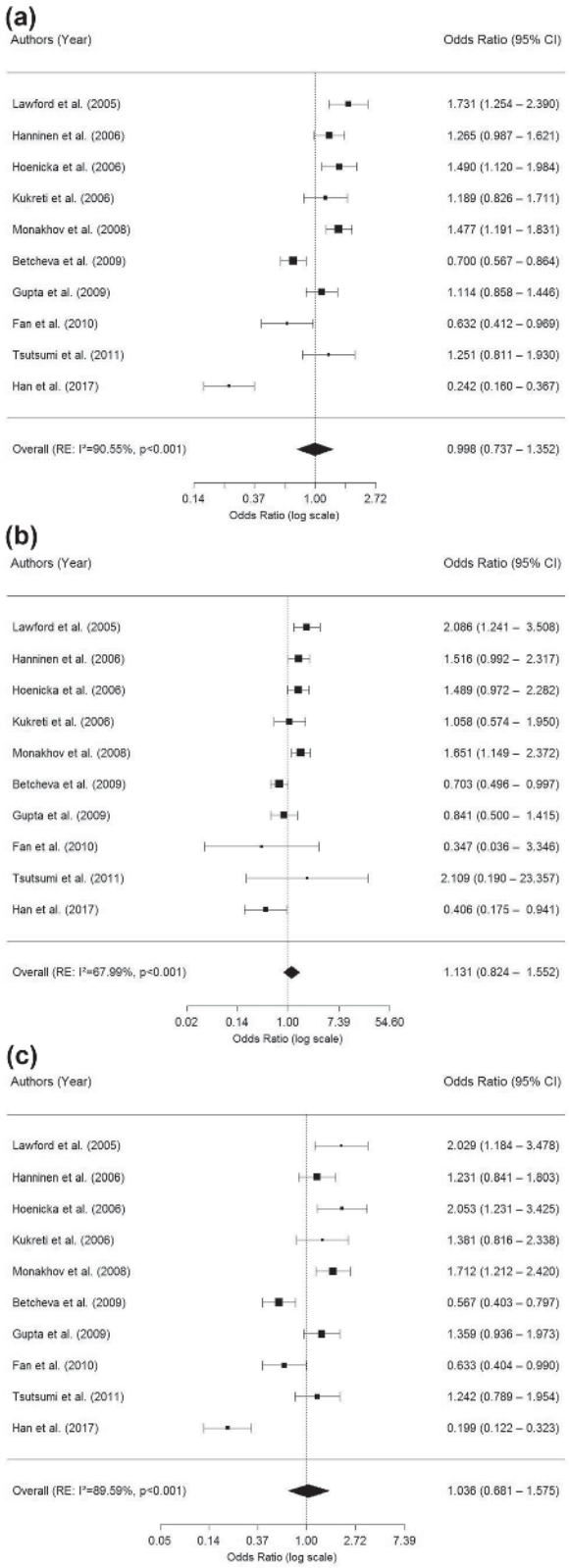

Figure 2. Forest plot of the risk of schizophrenia associated with rs6277 under (a) allelic, (b) dominant, and (c) recessive genetic models.

Table 7. Summary statistics of the meta-analysis findings.

Polymorphism	Analysis	Number of studies	Statistical model	OR	95% CI	Association test *P* value	I^2	Heterogeneity test *P* value	Egger's test *P* value
rs6277	Allelic model	10	Random effect	0.998	0.737–1.352	0.991	90.55%	< 0.0001	0.159
	Dominant model	10	Random effect	1.131	0.842–1.552	0.447	67.99%	0.0009	0.413
	Recessive model	10	Random effect	1.036	0.681–1.575	0.869	89.59%	< 0.0001	0.798
rs1799732	Allelic model	26	Random effect	0.966	0.822–1.135	0.672	75.27%	< 0.0001	0.624
	Dominant model	26	Random effect	0.952	0.800–1.133	0.578	72.61%	< 0.0001	0.948
	Recessive model	26	Random effect	1.060	0.744–1.511	0.748	35.14%	0.0409	0.057
rs1800497	Allelic model	20	Random effect	0.856	0.734–0.998	0.047	69.17%	< 0.0001	0.830
	Dominant model	20	Random effect	0.861	0.723–1.026	0.094	62.76%	< 0.0001	0.760
	Recessive model	20	Random effect	0.755	0.555–1.025	0.072	47.00%	0.011	0.217
rs1801028	Allelic model	31	Fixed effect	1.009	0.893–1.140	0.891	10.63%	0.2984	0.061
	Dominant model	31	Fixed effect	1.020	0.897–1.160	0.763	9.74%	0.3123	0.072
	Recessive model	31	Fixed effect	0.994	0.402–2.456	0.989	0	1	0.996

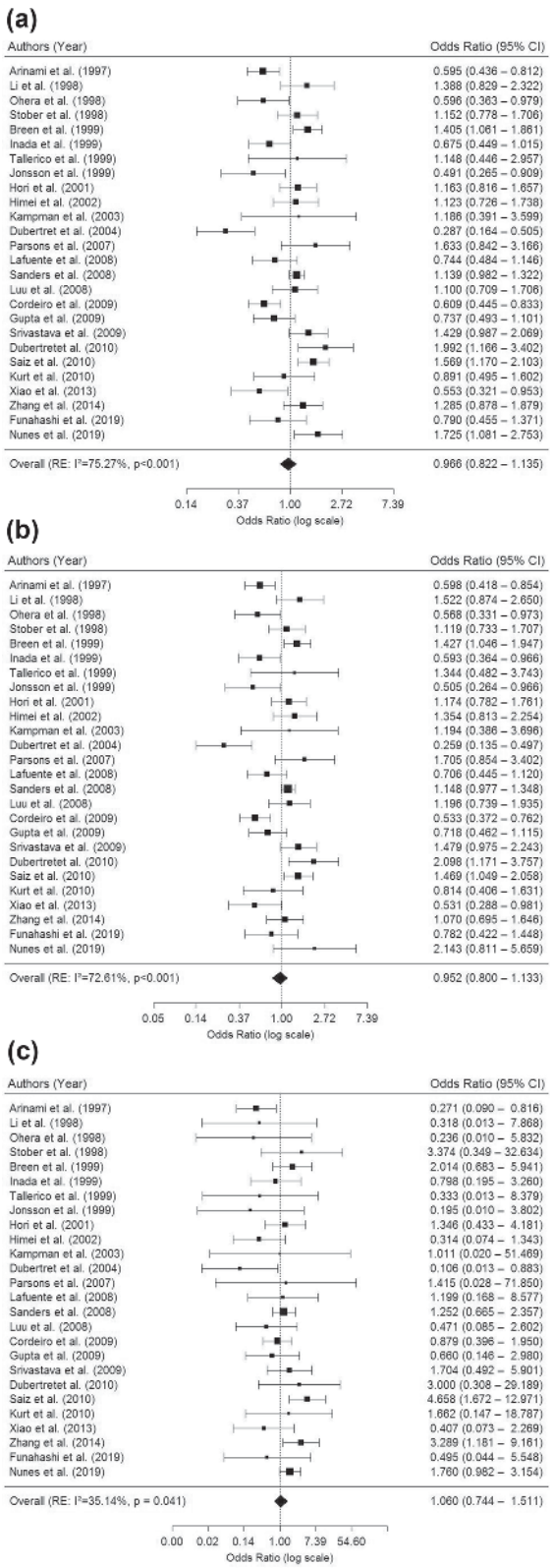

Figure 3. Forest plot of the risk of schizophrenia associated with rs1799732 under (a) allelic, (b) dominant, and (c) recessive genetic models.

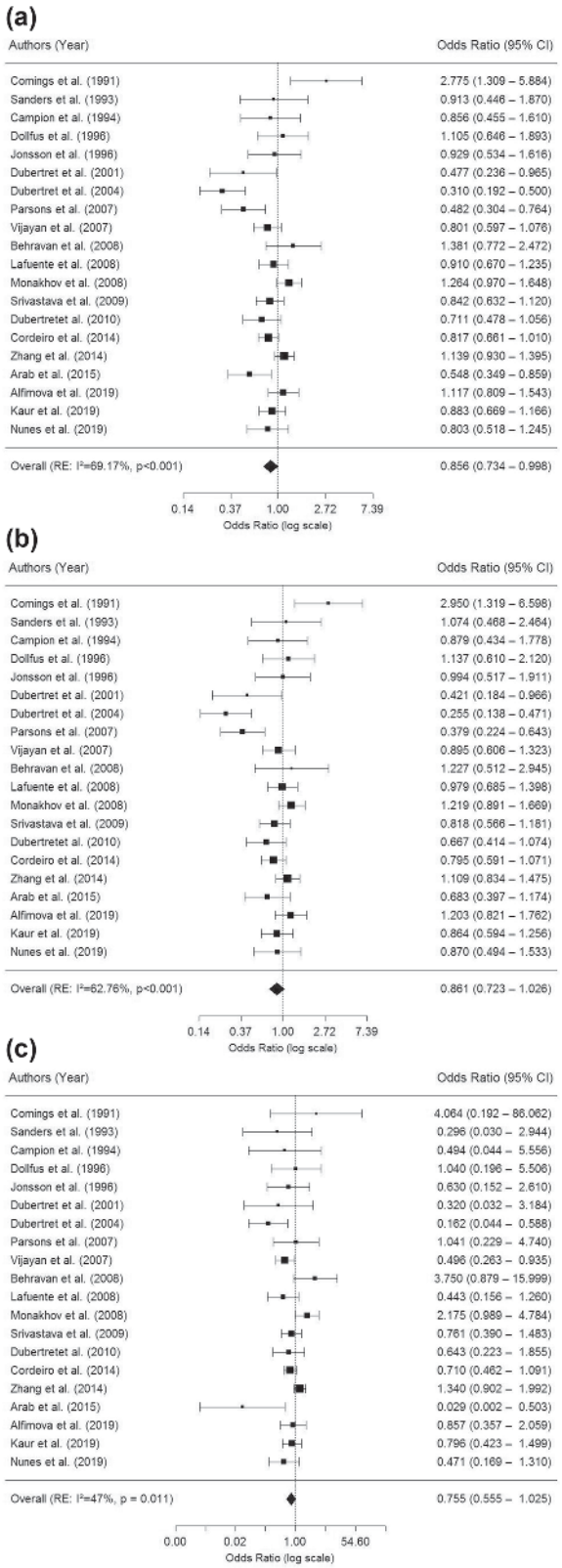

Figure 4. Forest plot of the risk of schizophrenia associated with rs1800497 under (a) allelic, (b) dominant, and (c) recessive genetic models.

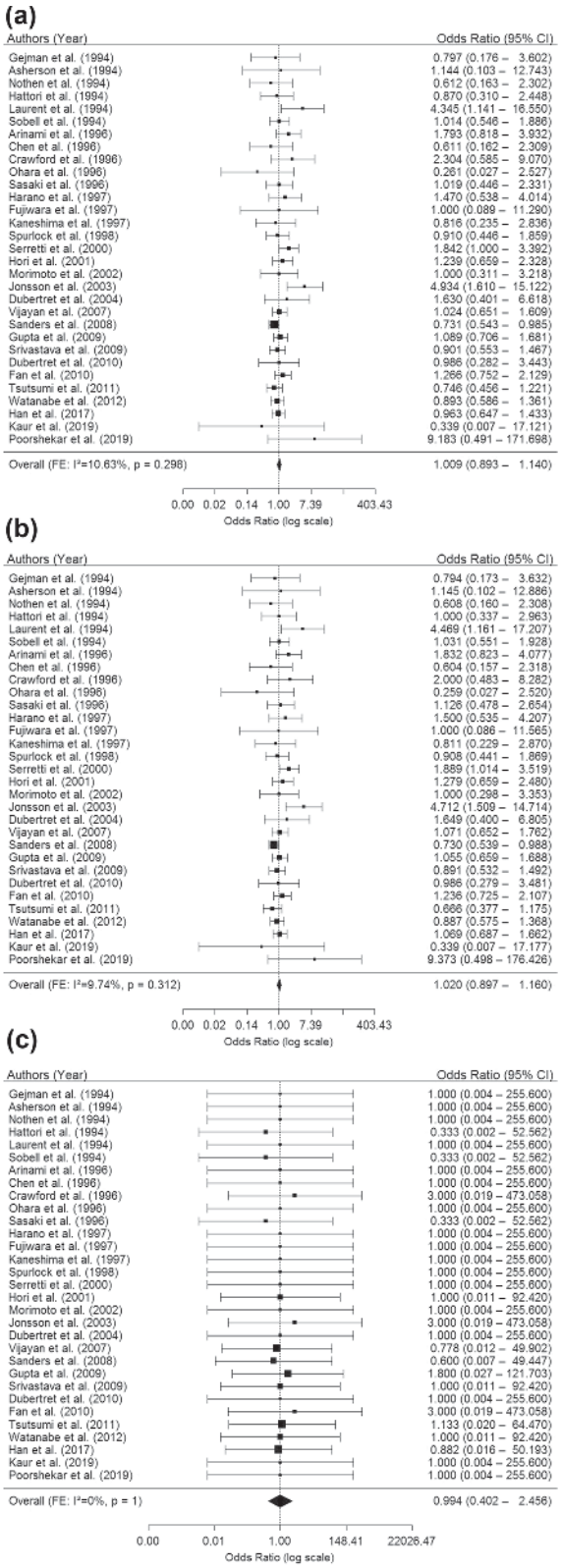

Figure 5. Forest plot of the risk of schizophrenia associated with rs1801028 under (a) allelic, (b) dominant, and (c) recessive genetic models.

studied genetic models. However, the included studies on rs1801028 did not show significant heterogeneity under all studied genetic models. Further, there was no evidence of publication bias according to Egger's regression test results (table 7). Funnel plots are also presented in figures 1–4 in electronic supplementary material.

Bioinformatics analysis

Analysis of the effect of rs1800497 on ANKK1 protein revealed that the substitution of glutamic acid by lysine caused by this mutation may decrease protein stability. Further, this polymorphism was found to lead to the gain of modifications sites for ubiquitination (ubi. score = −1.894) and methylation (meth. score = −0.834). The 3-D protein structure analysis of ANKK1 protein and the effects of this SNP on protein structure were also visualized (figure 6). The minimized total energy of wild type and mutant proteins were −20145.709 kcal/mol and −20125.746 kcal/mol, respectively. Further, the RMSD value was 0.008Å.

Discussion

Schizophrenia is a common psychiatric disorder occurring throughout the globe presenting with chronic or recurrent psychosis. Believed to result from a complex interaction between genetic and environmental factors, schizophrenia is among the top 10 illnesses in the global burden of disease (Murray *et al.* 1996). Considering the paramount importance of this disorder and the contradicting results of the previous studies investigating the genetic factors involved in the pathogenesis of this common psychiatric disease, we conducted this meta-analysis including 68 studies with 15,200 cases and 18,111 controls investigating the association of four SNPs involved in dopaminergic signalling (rs6277, rs1799732, rs1800497 and rs1801028) and schizophrenia. Our meta-analysis has the largest sample size among the meta-analysis conducted to date on this matter. Nevertheless, lack of meta-regression analyses was a potential limitation of this study. Different sources of the control population, various ethnic backgrounds, differences in the mean age of the control groups, and variations in gender ratios among the studies were potential sources of heterogeneity. Overall, our results indicated that rs1800497 polymorphism shows a protective effect against schizophrenia. However, no associations were found between the other three studied variants and risk of schizophrenia.

Other meta-analyses have previously investigated the association between genetic polymorphisms and the risk of schizophrenia (Glatt *et al.* 2004; Yao *et al.* 2015; He *et al.* 2016). Although our results showing the lack of association

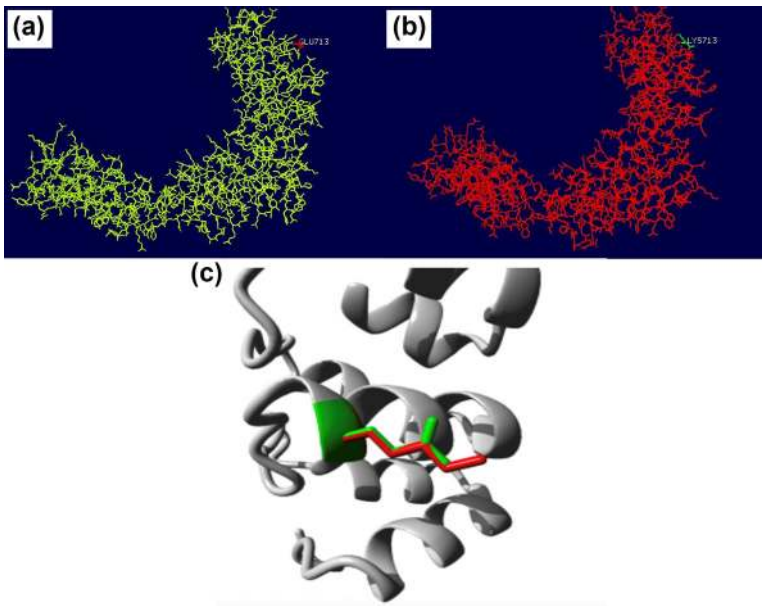

Figure 6. (a) Wild type and (b) mutant ANKK1 protein 3D structures. (c) Magnified view of protein. The protein is depicted in grey and the side chains of the wild-type and the mutant amino acids are illustrated in green and red, respectively.

of the mentioned SNPs with schizophrenia has largely been observed in the previous studies, the protective effect of rs1800497 against schizophrenia is a notable observation. This SNP which is also known as Taq1A was originally associated with the *DRD2* gene. However, it was later found to be located on the eighth exon of the *ANKK1* gene (Neville *et al.* 2004). This polymorphism which leads to an amino-acid substitution (p. Glu713Lys) in the 11th ankyrin repeat of the protein is postulated to modify substrate-binding specificity of the protein (Neville *et al.* 2004). Our bioinformatics analyses were also suggestive of decreased protein stability and gain of posttranslational modification sites for ubiquitination and methylation as a result of this polymorphism. The wild-type amino-acid in this position, glutamic acid, has a $–COO^-$ group which causes it to have a negative charge at physiologic pH while lysine has a positive charge. This substitution can, therefore, disrupt the salt bridges formed between the wild-type glutamic acid and lysine amino acids at positions 709 and 747 and therefore affect the function of the protein through disturbing the interaction between these domains. However, the structural analysis did not reveal any significant changes in the protein conformation as a result of this variant.

The minor allele (i.e. A1, rs1800497(T)) in this polymorphism has been found to be associated with decreased number of dopamine D2 receptor density/availability in the brain (Pohjalainen *et al.* 1998). In addition, the A1 allele has been demonstrated to be associated with increased aromatic L-amino acid decarboxylase activity in the striatum (Laakso *et al.* 2005). This enzyme is the final enzyme in dopamine biosynthesis and will, therefore, cause increased dopamine synthesis in those carrying Al allele. In addition, positron emission tomography (PET) studies have shown that this allele is associated with decreased mean relative glucose metabolic rate in dopaminergic human brain regions (Noble *et al.* 1997). On the other hand, this allele has been reported to be associated with alcoholism and anti-social behaviour in alcohol-dependent individuals (Ponce *et al.* 2003; Munafo *et al.* 2007). Considering the complex nature of schizophrenia and also the multitude of factors playing a part in the development of this disorder and the limited amount of information available about *ANKK1*, it is not clear if Taq1A polymorphism exerts its effect on dopaminergic signalling through affecting the *DRD2* gene or *ANKK1* itself directly modulates the dopaminergic signalling. Further functional studies on this variant could shed light on the role of this polymorphism in the pathogenesis of neuropsychiatric disorders.

Overall, our meta-analysis provides supporting evidence for the protective effect of rs1800497 (Taq1A) polymorphism against schizophrenia. However, further studies with larger sample sizes, particularly in ethnic populations underrepresented in this study (e.g. African populations) should be conducted to further investigate this association.

References

Abi-Dargham A., Rodenhiser J., Printz D., Zea-Ponce Y., Gil R., Kegeles L. S. *et al.* 2000 Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc. Natl. Acad. Sci. USA* **97**, 8104–8109.

Alfimova M. V., Golimbet V. E., Korovaitseva G. I., Aksenova E. V., Lezheiko T. V., Abramova L. I. *et al.* 2014 Association of the COMT and DRD2 genes with the ability of schizophrenia patients to understand the mental state of other people. *Neurosci. Behav. Physiol.* **45**, 12–18.

Alfimova M. V., Kondratyev N. V., Tomyshev A. S., Lebedeva I. S., Lezheiko T. V., Kaleda V. G. *et al*. 2019 Effects of a GWAS-supported schizophrenia variant in the DRD2 locus on disease risk, anhedonia, and prefrontal cortical thickness. *J. Mol. Neurosci.* **68**, 658–666.

Arab A. H. and Elhawary N. A. 2015 Association between ANKK1 (rs1800497) and LTA (rs909253) genetic variants and risk of schizophrenia. *Biomed. Res. Int*. **2015,** 821827.

Arinami T., Itokawa M., Enguchi H., Tagaya H., Yano S., Shimizu H. *et al*. 1994 Association of dopamine D2 receptor molecular variant with schizophrenia. *Lancet* **343**, 703–704.

Arinami T., Itokawa M., Aoki J., Shibuya H., Ookubo Y., Iwawaki A. *et al*. 1996 Further association study on dopamine D2 receptor variant S311C in schizophrenia and affective disorders. *Am. J. Med. Genet.* **67**, 133–138.

Arinami T., Gao M., Hamaguchi H. and Toru M. 1997 A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. *Hum. Mol. Genet.* **6**, 577–582.

Asherson P., Williams N., Roberts E., McGuffin M. and Owen M. 1994 DRD2 Ser311/Cys311 polymorphism in schizophrenia. *Lancet* **343**, 1045.

Beaulieu J. M. and Gainetdinov R. R. 2011 The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol. Rev.* **63**, 182–217.

Begg C. B. and Mazumdar M. 1994 Operating characteristics of a rank correlation test for publication bias. *Biometrics* **50**, 1088–1101.

Behravan J., Hemayatkar M., Toufani H. and Abdollahian E. 2008 Linkage and association of DRD2 gene TaqI polymorphism with schizophrenia in an Iranian population. *Arch. Iranian Med.* **11**, 252–256.

Betcheva E. T., Mushiroda T., Takahashi A., Kubo M., Karachanak S. K., Zaharieva I. T. *et al*. 2009 Case-control association study of 59 candidate genes reveals the DRD2 SNP rs6277 (C957T) as the only susceptibility factor for schizophrenia in the Bulgarian population. *J. Hum. Genet.* **54**, 98–107.

Breen G., Brown J., Maude S., Fox H., Collier D., Li T. *et al*. 1999 141 C Del/Ins polymorphism of the dopamine receptor 2 gene is associated with schizophrenia in a British population. *Am. J. Med. Genet.* **88**, 407–410.

Campion D., d'Amato T., Bastard C., Laurent C., Guedj F., Jay M. *et al*. 1994 Genetic study of dopamine D1, D2, and D4 receptors in schizophrenia. *Psychiatry Res.* **51**, 215–230.

Cardno A. G. and Gottesman II 2000 Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. *Am. J. Med. Genet.* **97**, 12–17.

Chen C. H., Chien S. H. and Hwu H. G. 1996 No association of dopamine D2 receptor molecular variant Cys311 and schizophrenia in Chinese patients. *Am. J. Med. Genet. b. Neuropsychiatr. Genet.* **67**, 418–420.

Comings D. E., Comings B. G., Muhleman D., Dietz G., Shahbahrami B., Tast D. *et al*. 1991 The dopamine-D2 receptor locus as a modifying gene in neuropsychiatric disorders. *Jama-J. Am. Med. Asso.* **266**, 1793–1800.

Cordeiro Q. and Vallada H. 2014 Association study between the Taq1A (rs1800497) polymorphism and schizophrenia in a Brazilian sample. *Arquivos De Neuro-Psiquiatria* **72**, 582–586.

Cordeiro Q., Siqueira-Roberto J., Zung S. and Vallada H. 2009 Association between the DRD2-141C insertion/deletion polymorphism and schizophrenia. *Arquivos De Neuro-Psiquiatria* **67**, 191–194.

Crawford F., Hoyne J., Cai X. G., Osborne A., Poston D., Zaglul J. *et al*. 1996 Dopamine DRD2/Cys311 is not associated with chronic schizophrenia. *Am. J. Med. Genet.* **67**, 483–484.

Dollfus S., Campion D., Vasse T., Preterre P., Laurent C., d'Amato T. *et al*. 1996 Association study between dopamine D1, D2, D3, and D4 receptor genes and schizophrenia defined by several diagnostic systems. *Biol. Psychiat.* **40**, 419–421.

Dubertret C., Gorwood P., Gouya L., Deybach J. C. and Ades J. 2001 Association and excess of transmission of a DRD2 haplotype in a sample of French schizophrenic patients. *Schizophrenia Res.* **49**, 203–212.

Dubertret C., Gouya L., Hanoun N., Deybach J. C., Ades J., Hamon M. *et al*. 2004 The 3 ' region of the DRD2 gene is involved in genetic susceptibility to schizophrenia. *Schizophrenia Res.* **67**, 75–85.

Dubertret C., Bardel C., Ramoz N., Martin P. M., Deybach J. C., Ades J. *et al*. 2010 A genetic schizophrenia-susceptibility region located between the ANKK1 and DRD2 genes. *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* **34**, 492–499.

Egger M., Davey Smith G., Schneider M. and Minder C. 1997 Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629–634.

Fan H., Zhang F. Q., Xu Y., Huang X. Z., Sun G. X., Song Y. Q. *et al*. 2010 An association study of DRD2 gene polymorphisms with schizophrenia in a Chinese Han population. *Neurosci. Lett.* **477**, 53–56.

Fujiwara Y., Yamaguchi K., Tanaka Y., Tomita H., Shiro Y., Kashihara K. *et al*. 1997 Polymorphism of dopamine receptors and transporter genes in neuropsychiatric diseases. *Eur. Neurol.* **38 (suppl 1)**, 6–10.

Funahashi Y., Yoshino Y., Yamazaki K., Ozaki Y., Mori Y., Mori T. *et al*. 2019 Analysis of methylation and -141C Ins/Del polymorphisms of the dopamine receptor D2 gene in patients with schizophrenia. *Psychiatr. Res.* **278**, 135–140.

Gejman P. V., Ram A., Gelernter J., Friedman E., Cao Q., Pickar D. *et al*. 1994 No structural mutation in the dopamine D2 receptor gene in alcoholism or schizophrenia: Analysis using denaturing gradient gel electrophoresis. *J. Am. Med. Asso.* **271**, 204–208.

Glatt S. J. and Jonsson E. G. 2006 The Cys allele of the DRD2 Ser311Cys polymorphism has a dominant effect on risk for schizophrenia: evidence from fixed- and random-effects meta-analyses. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **141B**, 149–154.

Glatt S. J., Faraone S. V. and Tsuang M. T. 2004 DRD2 -141C insertion/deletion polymorphism is not associated with schizophrenia: results of a meta-analysis. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **128B**, 21–23.

Gupta M., Chauhan C., Bhatnagar P., Gupta S., Grover S., Singh P. K. *et al*. 2009 Genetic susceptibility to Schizophrenia: Role of dopaminergic pathway gene polymorphisms. *Pharmacogenomics* **10**, 277–291.

Han J., Li Y. and Wang X. 2017 Potential link between genetic polymorphisms of catechol-O-methyltransferase and dopamine receptors and treatment efficacy of risperidone on schizophrenia. *Neuropsychiatr. Dis. Treat.* **13**, 2935–2943.

Hanninen K., Katila H., Kampman O., Anttila S., Illi A., Rontu R. *et al*. 2006 Association between the C957T polymorphism of the dopamine D2 receptor gene and schizophrenia. *Neurosci. Lett.* **407**, 195–198.

Harano M. 1997 Ser-311-Cys polymorphism of the dopamine D2 receptor gene and schizophrenia–an analysis of schizophrenic patients in Fukuoka. *Kurume Med. J.* **44**, 201–208.

Hattori M., Nanko S., Dai X. Y., Fukuda R. and Kazamatsuri H. 1994 Mismatch PCR RFLP detection of DRD2 SER311CYS polymorphism and schizophrenia. *Biochem. Biophys. Res. Commun.* **202**, 757–763.

He H., Wu H., Yang L., Gao F., Fan Y., Feng J. *et al*. 2016 Associations between dopamine D2 receptor gene polymorphisms and schizophrenia risk: a PRISMA compliant meta-analysis. *Neuropsychiatr. Dis. Treat.* **12**, 3129–3144.

Himei A., Koh J., Sakai J., Inada Y., Akabame K. and Yoneda H. 2002 The influence on the schizophrenic symptoms by the

DRD2Ser/Cys311 and-141C Ins/Del polymorphisms. *Psychiatr. Clini. Neurosci.* **56**, 97–102.

Hoenicka J., Aragüés M., Rodríguez-Jiménez R., Ponce G., Martínez I., Rubio G. *et al*. 2006 C957T DRD2 polymorphism is associated with schizophrenia in Spanish patients. *Acta Psychiatr. Scandinavica* **114**, 435–438.

Hori H., Ohmori O., Shinkai T., Kojima H. and Nakamura J. 2001 Association analysis between two functional dopamine D2 receptor gene polymorphisms and schizophrenia. *Am. J. Med. Genet.* **105**, 176–178.

Huedo-Medina T. B., Sanchez-Meca J., Marin-Martinez F. and Botella J. 2006 Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol. Methods* **11**, 193–206.

Inada T., Arinami and Yagi T. G. 1999 Association between a polymorphism in the promoter region of the dopamine D2 receptor gene and schizophrenia in Japanese subjects: replication and evaluation for antipsychotic-related features. *Int. J. Neuropsychopharmacol.* **2**, 181–186.

Itokawa M., Arinami T., Futamura N., Hamaguchi H. and Toru M. 1993 A structural polymorphism of human dopamine D2 receptor, D2(Ser311 → Cys). *Biochem. Biophys. Res. Commun.* **196**, 1369–1375.

Jonsson E., Brene S., Geijer T., Terenius L., Tylec A., Persson M. L. *et al*. 1996 A search for association between schizophrenia and dopamine-related alleles. *Eur. Arch. Psychiatry. Clin. Neurosci.* **246**, 297–304.

Jonsson E. G., Nothen M. M., Neidt H., Forslund K., Rylander G., Mattila-Evenden M. *et al*. 1999 Association between a promoter polymorphism in the dopamine D2 receptor gene and schizophrenia. *Schizophrenia Res.* **40**, 31–36.

Jonsson E. G., Sillen A., Vares M., Ekholm B., Terenius L. and Sedvall G. C. 2003 Dopamine D2 receptor gene Ser311Cys variant and schizophrenia: association study and meta-analysis. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.* **119B**, 28–34.

Kahn R. S., Sommer I. E., Murray R. M., Meyer-Lindenberg A., Weinberger D. R., Cannon T. D. *et al*. 2015 Schizophrenia. *Nat. Rev. Dis. Primers* **1**, 15067.

Kampman O., Anttila S., Illi A., Lehtimaki T., Mattila K. M., Roivas M. *et al*. 2003 Dopamine receptor D2–141C insertion/deletion polymorphism in a Finnish population with schizophrenia. *Psychiat. Res.* **121**, 89–92.

Kaneshima M., Higa T., Nakamoto H. and Nagamine M. 1997 An association study between the Cys311 variant of dopamine D2 receptor gene and schizophrenia in the Okinawan population. *Psychiatr. Clin. Neurosci.* **51**, 379–381.

Kaur G., Chavan B. S., Gupta D., Sinhmar V., Prasad R., Tripathi A. *et al*. 2019a An association study of dopaminergic (DRD2) and serotoninergic (5-HT2) gene polymorphism and schizophrenia in a north Indian population. *Asian J. Psychiatr.* **39**, 178–184.

Kaur G., Singh Chavan B., Gupta D., Sinhmar V., Prasad R., Tripathi A. *et al*. 2019b An association study of dopaminergic (DRD2) and serotoninergic (5-HT2) gene polymorphism and schizophrenia in a north Indian population. *Asian J. Psychiatr.* **39**, 178–184.

Koeneke A., Ponce G., Troya-Balseca J., Palomo T., and Hoenicka J. 2020 Ankyrin repeat and kinase domain containing 1 gene, and addiction vulnerability. *Int. J. Mol. Sci*. **21**.

Kukreti R., Tripathi S., Bhatnagar P., Gupta S., Chauhan C., Kubendran S. *et al*. 2006 Association of DRD2 gene variant with schizophrenia. *Neurosci. Lett.* **392**, 68–71.

Kurt H., Dikmen M., Basaran A., Yenilmez C., Ozdemir F., Degirmenci I. *et al*. 2011 Dopamine D2 receptor gene -141C insertion/deletion polymorphism in Turkish schizophrenic patients. *Mol. Biol. Rep.* **38**, 1407–1411.

Laakso A., Pohjalainen T., Bergman J., Kajander J., Haaparanta M., Solin O. *et al*. 2005 The A1 allele of the human D2 dopamine receptor gene is associated with increased activity of striatal L-amino acid decarboxylase in healthy subjects. *Pharmacogenet. Genomics* **15**, 387–391.

Lafuente A., Bernardo M., Mas S., Crescenti A., Aparici M., Gasso P. *et al*. 2008 141C Ins/Del polymorphism of the dopamine D2 receptor gene is associated with schizophrenia in a Spanish population. *Psychiatr. Genet.* **18**, 122–127.

Laurent C., Bodeau-Pean S., Campion D., d'Amato T., Jay M., Dollfus S. *et al*. 1994 No major role for the dopamine D2 receptor Ser–>Cys311 mutation in schizophrenia. *Psychiatr. Genet.* **4**, 229–230.

Lawford B. R., Young R. M., Swagell C. D., Barnes M., Burton S. C., Ward W. K. *et al*. 2005 The C/C genotype of the C957T polymorphism of the dopamine D2 receptor is associated with schizophrenia. *Schizophrenia Res.* **73**, 31–37.

Li T., Arranz M., Aitchison K. J., Bryant C., Liu X., Kerwin R. W. *et al*. 1998 Case-control, haplotype relative risk and transmission disequilibrium analysis of a dopamine D2 receptor functional promoter polymorphism in schizophrenia. *Schizophrenia Res.* **32**, 87–92.

Liberati A., Altman D. G., Tetzlaff J., Mulrow C., Gotzsche P. C., Ioannidis J. P. *et al*. 2009 The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* **6**, e1000100.

Luu S. U., Liao H. M., Hung T. W., Liu B. Y., Cheng M. C., Liao D. L. *et al*. 2008 Mutation analysis of adenosine A2a receptor gene and interaction study with dopamine D2 receptor gene in schizophrenia. *Psychiatr. Genet.* **18**, 43.

Monakhov M., Golimbet V., Abramova L., Kaleda V. and Karpov V. 2008 Association study of three polymorphisms in the dopamine D2 receptor gene and schizophrenia in the Russian population. *Schizophrenia Res.* **100**, 302–307.

Morimoto K., Miyatake R., Nakamura M., Watanabe T., Hirao T. and Suwaki H. 2002 Delusional disorder: molecular genetic evidence for dopamine psychosis. *Neuropsychopharmacology* **26**, 794–801.

Munafo M. R., Matheson I. J. and Flint J. 2007 Association of the DRD2 gene Taq1A polymorphism and alcoholism: a meta-analysis of case-control studies and evidence of publication bias. *Mol. Psychiatr.* **12**, 454–461.

Murray C. J. L., Lopez A. D., World Health O., World B., Harvard School of Public H. 1996 The Global burden of disease : a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020: summary/edited by Christopher J. L. Murray, Alan D. Lopez. World Health Organization, Geneva.

Nanko S., Hattori M., Dai X. Y., Fukuda R. and Kazamatsuri H. 1994 DRD2 Ser311/Cys311 polymorphism in schizophrenia. *Lancet* **343**, 1044.

Neville M. J., Johnstone E. C. and Walton R. T. 2004 Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. *Hum. Mutat.* **23**, 540–545.

Noble E. P., Gottschalk L. A., Fallon J. H., Ritchie T. L. and Wu J. C. 1997 D2 dopamine receptor polymorphism and brain regional glucose metabolism. *Am. J. Med. Genet.* **74**, 162–166.

Nothen M. M., Wildenauer D., Cichon S., Albus M., Maier W., Minges J. *et al*. 1994 Dopamine D2 receptor molecular variant and schizophrenia. *Lancet* **343**, 1301–1302.

Nunes F. P., Freitas P., Santos L. and Machado R. 2019 Frequency of ANKK1, DRD2, DRD3 gene polymorphisms in refractory schizophrenia patients. *Genet. Mol. Res*. **18**.

Ohara K., Nakamura Y., Xie D. W., Ishigaki T., Deng Z. L., Tani K. *et al*. 1996 Polymorphisms of dopamine D2-like (D2, D3, and D4) receptors in schizophrenia. *Biol. Psychiatry* **40**, 1209–1217.

Ohara K., Nagai M., Tani K., Nakamura Y., Ino A. and Ohara K. 1998 Functional polymorphism of -141C Ins/Del in the dopamine D2 receptor gene promoter and schizophrenia. *Psychiatry. Res.* **81**, 117–123.

Parsons M. J., Mata I., Beperet M., Iribarren-Iriso F., Arroyo B., Sainz R. *et al*. 2007 A dopamine D2 receptor gene-related polymorphism is associated with schizophrenia in a Spanish population isolate. *Psychiatr. Genet.* **17**, 159–163.

Pohjalainen T., Rinne J. O., Nagren K., Lehikoinen P., Anttila K., Syvalahti E. K. *et al*. 1998 The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. *Mol. Psychiatry* **3**, 256–260.

Ponce G., Jimenez-Arriero M. A., Rubio G., Hoenicka J., Ampuero I., Ramos J. A. *et al*. 2003 The A1 allele of the DRD2 gene (TaqI A polymorphisms) is associated with antisocial personality in a sample of alcohol-dependent patients. *Eur. Psychiatr.* **18**, 356–360.

Poorshekar S., Firoozfar A., Dehghani M., Yassini Ardekani S. M. and Kalantar S. M. 2019 Study of the association between DRD2 Gene Ser311Cys and GSTM1 Gene polymorphism in Schizophrenia. *J. Shahid Sadoughi Univer. Med. Sci.* **27**, 1602–1611.

Saiz P. A., Garcia-Portilla M. P., Arango C., Morales B., Arias B., Corcoran P. *et al*. 2010 Genetic polymorphisms in the dopamine-2 receptor (DRD2), dopamine-3 receptor (DRD3), and dopamine transporter (SLC6A3) genes in schizophrenia: Data from an association study. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **34**, 26–31.

Sanders A. R., Rinconlimas D. E., Chakraborty R., Grandchamp B., Hamilton J. D., Fann W. E. *et al*. 1993 association between genetic-variation at the porphobilinogen deaminase gene and schizophrenia. *Schizophrenia Res.* **8**, 211–221.

Sanders A. R., Duan J., Levinson D. F., Shi J., He D., Hou C. *et al*. 2008 No significant association of 14 candidate genes with schizophrenia in a large European ancestry sample: Implications for psychiatric genetics. *Am. J. Psychiatr.* **165**, 497–506.

Sasaki T., Macciardi F. M., Badri F., Verga M., Meltzer H. Y., Lieberman J. *et al*. 1996 No evidence for association of dopamine D2 receptor variant (Ser311/Cys311) with major psychosis. *Am. J. Med. Genet.* **67**, 415–417.

Schizophrenia Working Group of the Psychiatric Genomics C 2014 Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421–427.

Seeman P. 1987 Dopamine receptors and the dopamine hypothesis of schizophrenia. *Synapse* **1**, 133–152.

Serretti A., Lattuada E., Lorenzi C., Lilli R. and Smeraldi E. 2000 Dopamine receptor D2 Ser/Cys 311 variant is associated with delusion and disorganization symptomatology in major psychoses. *Mol. Psychiatry* **5**, 270–274.

Shaikh S., Collier D., Arranz M., Ball D., Gill M. and Kerwin R. 1994 DRD2 Ser311/Cys311 polymorphism in schizophrenia. *Lancet* **343**, 1045–1046.

Sobell J., Sigurdson D. C., Heston L. and Sommer S. 1994 S311C D2DR variant: no association with schizophrenia. *Lancet* **344**, 621–622.

Spurlock G., Williams J., McGuffin P., Aschauer H. N., Lenzinger E., Fuchs K. *et al*. 1998 European multicentre association study of schizophrenia: A study of the DRD2 Ser311Cys and DRD3 Ser9Gly polymorphisms. *Am. J. Med. Genet.* **81**, 24–28.

Srivastava V., Deshpande S. N. and Thelma B. K. 2010 Dopaminergic pathway gene polymorphisms and genetic susceptibility to schizophrenia among north Indians. *Neuropsychobiology* **61**, 64–70.

Stang A. 2010 Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur. J. Epidemiol.* **25**, 603–605.

Stober G., Jatzke S., Heils A., Jungkunz G., Knapp M., Mossner R. *et al*. 1998 Insertion/deletion variant (-141C Ins/Del) in the 5' regulatory region of the dopamine D2 receptor gene: lack of association with schizophrenia and bipolar affective disorder Short Communication. *J. Neural. Transm. (vienna)* **105**, 101–109.

Tallerico T., Ulpian C. and Liu I. S. C. 1999 Dopamine D-2 receptor promoter polymorphism: no association with schizophrenia. *Psychiatr. Res.* **85**, 215–219.

Tanaka T., Igarashi S., Onodera O., Tanaka H., Fukushima N., Takahashi M. *et al*. 1996 Lack of association between dopamine D2 receptor gene Cys311 variant and schizophrenia. *Am. J. Med. Genet.* **67**, 208–211.

Tsutsumi A., Glatt S. J., Kanazawa T., Kawashige S., Uenishi H., Hokyo A. *et al*. 2011 The genetic validation of heterogeneity in schizophrenia. *Behav. Brain Funct.* **7**, 5.

van Rossum J. M. 1966 The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. *Arch. Int. Pharmacodyn. Ther.* **160**, 492–494.

Venselaar H., Te Beek T. A., Kuipers R. K., Hekkelman M. L. and Vriend G. 2010 Protein structure analysis of mutations causing inheritable diseases e-Science approach with life scientist friendly interfaces. *BMC Bioinformatics* **11**, 548.

Verga M., Macciardi F., Pedrini S., Cohen S. and Smeraldi E. 1997 No association of the Ser/Cys311 DRD2 molecular variant with schizophrenia using a classical case control study and the haplotype relative risk. *Schizophrenia Res.* **25**, 117–121.

Viechtbauer W. 2010 Conducting meta-analyses in R with the metafor package. 2010 **36,** 48.

Vijayan N. N., Bhaskaran S., Koshy L. V., Natarajan C., Srinivas L., Nair C. M. *et al*. 2007 Association of dopamine receptor polymorphisms with schizophrenia and antipsychotic response in a South Indian population. *Behav. Brain Funct.* **3**, 12.

Wang Y., Liu L., Xin L., Fan D., Ding N., Hu Y. *et al*. 2016 The -141C Ins/Del and Taq1A polymorphism in the dopamine D2 receptor gene may confer susceptibility to schizophrenia in Asian populations. *J. Clin. Neurosci.* **30**, 1–7.

Watanabe Y., Nunokawa A., Kaneko N., Shibuya M., Egawa J., Fukui N. *et al*. 2012 Case-control study and meta-analysis of Ser311Cys polymorphism in the DRD2 gene demonstrate lack of association with risk for schizophrenia in the Japanese population. *Genet. Mol. Res.* **11**, 1142–1145.

Watanabe Y., Shibuya M. and Someya T. 2015 DRD2 Ser311Cys polymorphism and risk of schizophrenia. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.* **168B**, 224–228.

Xiao L., Shen T., Peng D. H., Shu C., Jiang K. D. and Wang G. H. 2013 Functional -141C Ins/Del polymorphism in the dopamine D2 receptor gene promoter and schizophrenia in a Chinese Han population. *J. Int. Med. Res.* **41**, 1171–1178.

Yang Y., Peng X., Ying P., Tian J., Li J., Ke J. *et al*. 2019 AWESOME: a database of SNPs that affect protein post-translational modifications. *Nucleic Acids Res.* **47**, D874–D880.

Yao J., Pan Y. Q., Ding M., Pang H. and Wang B. J. 2015 Association between DRD2 (rs1799732 and rs1801028) and ANKK1 (rs1800497) polymorphisms and schizophrenia: a meta-analysis. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.* **168B**, 1–13.

Zhang C., Zhang J. T., Fan J., Cheng W. H., Du Y. S., Yu S. Y. *et al*. 2014 Identification of ANKK1 rs1800497 Variant in schizophrenia: new data and meta-analysis. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.* **165**, 564–571.

Zhang X. C., Ding M., Adnan A., Liu Y., Liu Y. P., Xing J. X. *et al*. 2019a No association between polymorphisms in the promoter region of dopamine receptor D2 gene and schizophrenia in the northern Chinese Han population: A case-control study. *Brain Behav.* **9**, e01193.

Zhang X. C., Ding M., Adnan A., Liu Y., Liu Y. P., Xing J. X. *et al*. 2019b No association between polymorphisms in the promoter region of dopamine receptor D2 gene and schizophrenia in the northern Chinese Han population: a case-control study. *Brain Behav.* **9**, 8.

Corresponding editor: Analabha Basu