A meta-analysis of the association between RGS4 gene polymorphisms and schizophrenia

Feng-ling Xu
China Medical University
Xue Wu
China Medical University
Li Liu
First Hospital of China Medical University
Xi Xia
China Medical University
Ya Li
China Medical University
Jun Yao
China Medical University
Bao-jie Wang (wangbj77@163.com)
China Medical University https://orcid.org/0000-0003-1931-423X

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Abstract

Background: Schizophrenia is a complex brain disorder, the pathogenesis of which remains unclear. Regulator of G-protein signaling 4 (RGS4) is regarded as a candidate gene for schizophrenia risk. The association between the RGS4 gene and the risk of schizophrenia is complicated and controversial, thus, an updated meta-analysis is needed. Methods: A search strategy using Medical Subject Headings was developed in English (PubMed, SZGene) and Chinese (CNKI, Wanfang and Weipu) databases. Inclusion and exclusion criteria were used to screen for eligible studies. Parameters, such as P -value of Hardy – Weinberg equilibrium (P HWE), odds ratios (ORs), 95% confidence intervals (CIs), P -values of association (P z ,), heterogeneity (P h), and publication bias (P e), were analyzed by the Stata software using a random effects model. Subgroup analyses were performed to detect heterogeneity. Results: There were 15 articles regarding rs10917670 (8,046 cases and 8,837 controls), 16 regarding rs951436 (8,990 cases and 10,568 controls), 15 regarding rs951439 (7,995 cases and 8,646 controls), 15 regarding rs2661319 (8,320 cases and 9,440 controls), and 4 regarding rs10759 (2,752 cases and 2,866 controls). The frequencies of rs10917670 and rs951439 were not significantly different between the case and control groups ($p > 0.05$). As shown by the East Asian and hospital-based subgroup analyses, the genotype TT of rs951436 might be related to the risk of schizophrenia. The genotypes CC+CT of rs2661319 and CC+CA of rs10759 were statistically different between the two groups, and the East Asian population contributed to these differences. Conclusion: The genotypes CC+CT of rs2661319 and CC+CA of rs10759 might be associated with the risk of schizophrenia.

1. Introduction

Schizophrenia is a complex brain disorder, the pathogenesis of which remains unclear [1]. It has been shown that schizophrenia is caused by both genetic and environmental factors [2], and genetic factors play an important role to the etiology of schizophrenia [3, 4]. Regulator of G-protein signaling (RGS) proteins control the duration and timing of intracellular signaling of many G-protein coupled receptors (GPCRs). The major mechanism by which RGS proteins negatively regulate G proteins is via their GTPase accelerating activity [5]. RGS4 is known to play a fundamental role in neurotransmission and neuronal differentiation, in addition to axonogenesis during embryogenesis [6]. RGS4 regulation of G-protein activity, may inhibit the interaction between neurotransmitters and their receptors, leading to dysfunction of glutamatergic neurotransmission [7], which is classically related to the etiology of psychotic disorders [8]. Schwarz et al. [6] suggested that the RGS4 gene, localized to chromosome 1q23, might be an important part of a larger biological system contributing to schizophrenia risk. Mirnics et al. [9] showed that RGS4 expression was down regulated in schizophrenia [10, 11]. However, the association between RGS4 and the risk of schizophrenia remains controversial [12–15].

Meta-analysis is a useful tool for the detection of disease – gene relationships [16]. In the Chinese Han population, one meta-analysis showed no association between the RGS4 gene and the risk of schizophrenia [15]; however, in another meta-analysis, the SNP, rs951436, was found to be associated with the risk of schizophrenia [17]. Therefore, the association between RGS4 and the risk of schizophrenia remains complicated and controversial [17–19]. Additional articles have since been published; thus, an updated meta-analysis is needed. Here, we conducted an updated meta-analysis to detect the association between RGS4 gene polymorphisms and the risk of schizophrenia.

2. Materials And Methods

2.1. Literature search

The systematic review and meta-analysis were conducted in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [20]. A search was performed in English (PubMed, SZGene) and Chinese (CNKI, Wanfang and Weipu) databases with the following keywords: “the regulator of G-protein signaling 4” or “RGS4" and "schizophrenia". References to related articles were also reviewed for further data.

2.2. Identification and eligibility of relevant studies

The inclusion criteria were: 1) studies with a case–control design; 2) involvement of patients with schizophrenia; 3) available allele or genotype frequencies; and 4) published before February 20th, 2019. The authors were emailed if there was no genotype frequency mentioned in the article. The exclusion criteria were: 1) family-based studies; 2) no control group data; 3) no detailed genotype frequency data after emailing the authors; and 4) duplicate samples [21]. Information regarding the author, year, country, ethnicity, controls source, mean age of the control group, number of samples, diagnostic criteria, gender index the of cases and controls, and genotypes of the cases and controls were collected.

2.3. Statistical analysis

The meta-analysis was conducted using Stata version 10.0 (Stata Corp., College Station, TX). In the control group, the P-value of Hardy – Weinberg equilibrium (P_{HWE}) was calculated. Parameters, such as the odds ratios (ORs), 95% confidence intervals (CIs), and P-values of association ($P_{z,}$), were calculated to detect the association in five genetic models [22], using the random effects model [21, 23]. The heterogeneity of the studies (P_h) was determined by Cochran's chi-square-based Q-statistic test. To assess the heterogeneity, subgroup analyses by ethnicity and control source were performed [24]. The studies were classified by control source into community-based (participants from the general population) and hospital-based (participants from a hospital) groups [25]. The Egger's test was conducted to detect the publication bias (P_e), which could be visualized using a funnel plot. To assess the impact of each study on the pooled results, sensitivity analysis was performed by removing single studies in turn. The power was calculated using the PS program [26]. The threshold for statistical significance was $P < 0.05$ in all tests.

3. Results

3.1. Description of studies

A total of 106 English and 43 Chinese articles were found, with 20 articles being eligible for analysis following exclusion (Fig. 1). The data regarding the genotypes in [11, 14, 27] were unavailable. Table 1 described the detailed characteristics of the 20 eligible studies. There were 15 articles regarding rs10917670 [15, 18, 28–40], 16 regarding rs951436 [12, 13, 15, 18, 28, 30–34, 36–39, 41, 42], 15 regarding rs951439 [15, 18, 28, 30–34, 36–40, 42, 43], 15 regarding rs2661319 [15, 18, 28–39, 42] and 4 regarding rs10759 [13, 36, 38, 40]. There were less than 4 articles regarding other SNPs of the RGS4 gene; therefore, these were not included in the present meta-analysis. The SNPs, rs10917670, rs951436, and rs951439, are located in the 5' regulatory region, rs2661319 is located in the first intron, and rs10759 is located in the 3' untranslated region (3' UTR).

Table 1

Baseline characteristics of eligible studies in the present meta-analysis

Author	Year	Country	Ethnicity	controls source	Mean age of control group	Diagnostic criteria	Gender index (case)	Gender index (control)
Réthelyi	2010	Hungarian	Caucasian	community-based	39.9 ± 15.0	DSM-IV	1.174	1.381
Jönsson	2012	Scandinavian	Caucasian	community-based	44.1 ± 11.8	DSM-III	0.712	0.736
So	2008	China	East Asia	hospital-based	41.9 ± 9.79	DSM-IV	0.404	0.691
Guo	2006	China	East Asia	community-based	25.87 ± 7.58	DSM-IV	0.767	0.811
Kampman	2006	Finland	Caucasian	community-based	44.5 ± 11.1	DSM-IV	0.711	0.852
Rizig	2006	UK	Caucasian	community-based		ICD10		
Zhang	2005	UK	Caucasian	community-based		DSM-IV	0.389	0.754
Sobell	2005	USA	Caucasian	hospital-based	66.2 ± 10.6	DSM-III-R		
Cordeiro	2005	Brazil	Caucasian	community-based		DSM-IV		
Prasad	2005	USA	Caucasian	community-based	24.74 ± 7.23	DSM-IV	0.429	0.929
Morris	2004	Irish	Caucasian	community-based		DSM-IIIR		
Williams	2004	UK	Caucasian	community-based	44.93 ± 12.04	DSM-IV	0.468	0.488
Bakker	2007	Dutch	Caucasian	community-based		DSM-IV		
Betcheva	2009	Bulgaria	Caucasian	community-based	50.5 ± 16.0	DSM-IV	1.041	0.923
Chowdari	2002	USA	Caucasian	community-based		DSM-IV		
Sanders	2008	USA, Australia	Caucasian	community-based		DSM-IV	0.441	
Wood	2007	US	Caucasian	community-based		DSM-IV		
Ishiguro	2006	Japan	East Asia	community-based	49.0 ± 14.3	DSM-IV	0.818	0.882

Author	Year	Country	Ethnicity	controls source	Mean age of control group	Diagnostic criteria	Gender index (case)	Gender index (control)
Yue	2007	China	East Asia	community-based	30 ± 8	ICD-10	0.92	0.857
Qian	2005	China	East Asia	community-based	30.8 ± 15.78	DSM-IIIR	0.936	0.79

3.2. Results of data analysis

3.2.1. There is no association between rs10917670 and the risk of schizophrenia

Genotype frequency of 8,046 cases and 8,837 controls was used to perform pooled and subgroup analyses using the random effects model (Table 2). Results of the pooled and subgroup analyses were summarized in Tables 3 and 4. Using the recessive model (Fig. 2), no association was found between rs10917670 and the risk of schizophrenia in the pooled analysis (P_z = 0.946, OR = 0.997, 95%CI = 0.926 − 1.074). No association was detected in the subgroup analyses by ethnicity or control source. Moreover, no significant heterogeneity was observed in the pooled or subgroup analyses.

Table 2

Genotype distribution and allele frequency of rs10917670

Author	Year	Genotype distribution							Allele frequency			
		Case, n			Control, n				Case, n		Control, n	
		AA	AG	GG	AA	AG	GG	P_{HWE}	A	G	A	G
Réthelyi	2010	60	139	81	42	113	75	0.961	259	301	197	263
So	2008	94	216	132	107	249	145	0.996	404	480	461	541
Guo	2006	49	146	91	55	140	89	0.997	244	328	250	318
Zhang	2005	107	284	189	94	295	231	0.991	498	662	483	757
Sobell	2005	90	273	205	129	335	225	0.827	453	683	593	785
Cordeiro	2005	45	140	85	101	293	179	0.315	230	310	495	651
Prasad	2005	9	13	6	7	7	13	0.018	31	25	21	33
Morris	2004	40	119	90	50	115	66	0.994	199	299	215	247
Williams	2004	116	338	231	114	330	247	0.831	570	800	558	824
Bakker	2007	82	135	40	205	214	82	0.042	299	215	624	378
Betcheva	2009	37	92	56	28	88	68	0.957	166	204	144	224
Chowdari	2002	31	69	46	21	45	32	0.489	131	161	87	109
Sanders	2008	317	906	647	357	977	669	0.993	1540	2200	1691	2315
Ishiguro	2006	392	866	556	367	895	553	0.888	1650	1978	1629	2001
Yue	2007	49	196	141	68	185	137	0.684	294	478	324	459

Table 3

Pooled association of RGS4 polymorphisms with schizophrenia

Loci	Genetic model	Studies (n)	Statistical	OR	95% CI	P_z	I^2	P_h	P_e
rs10917670	allele contrast	15	Random	1.011	0.929–1.052	0.72	39.40	0.058	0.553
	Homozygous codominant	15	Random	1.022	0.906–1.153	0.725	33	0.104	0.663
	Heterozygous codominant	15	Random	1.048	0.954–1.150	0.332	13.3	0.304	0.514
	Dominant	15	Random	1.045	0.944–1.157	0.393	29.4	0.136	0.932
	Recessive	15	Random	0.997	0.926–1.074	0.946	13	0.308	0.198
rs951436	allele contrast	16	Random	1.039	0.967–1.116	0.298	61.5	0.001	0.413
	Homozygous codominant	16	Random	0.971	0.852–1.107	0.664	53.2	0.006	0.795
	Heterozygous codominant	16	Random	1.012	0.943–1.086	0.741	0	0.601	0.86
	Dominant	16	Random	0.998	0.918–1.085	0.964	26.4	0.158	0.931
	Recessive	16	Random	0.965	0.870–1.072	0.51	52.5	0.007	0.619
rs951439	allele contrast	15	Random	1.031	0.890–1.054	0.461	69.6	0	0.276
	Homozygous codominant	14	Random	1.018	0.886–1.170	0.803	47.7	0.024	0.229
	Heterozygous codominant	14	Random	1.036	0.952–1.127	0.416	0	0.944	0.674
	Dominant	14	Random	1.036	0.952–1.128	0.414	6.1	0.385	0.324
	Recessive	14	Random	0.998	0.9051.100	0.969	44.3	0.038	0.139
rs2661319	allele contrast	15	Random	1.068	1.009–1.130	0.023	32.4	0.109	0.125
	Homozygous codominant	15	Random	1.126	1.009–1.256	0.034	27.2	0.156	0.211
	Heterozygous codominant	15	Random	1.066	0.992–1.145	0.082	0	0.681	0.016
	Dominant	15	Random	1.087	1.016–1.164	0.016	0	0.513	0.027
	Recessive	15	Random	1.101	1.002–1.211	0.046	34.9	0.09	0.424

Loci	Genetic model	Studies (n)	Statistical	OR	95% CI	P_z	I^2	P_h	P_e
rs10759	allele contrast	4	Random	1.148	0.728–0.997	0.046	59.2	0.062	0.786
	Homozygous codominant	4	Random	1.427	0.969–2.101	0.072	63.2	0.043	0.742
	Heterozygous codominant	4	Random	1.133	0.952–1.350	0.161	0	0.865	0.4
	Dominant	4	Random	1.226	1.038–1.448	0.016	0	0.516	0.431
	Recessive	4	Random	1.254	0.974–1.615	0.079	67.1	0.028	0.947

Table 4
Subgroup association of RGS4 polymorphisms with schizophrenia

Loci	Subgroup analysis	Studies (n)	OR	95% CI	P_z	I^2	P_h
rs10917670	Caucasians	11	0.971	0.865–1.090	0.618	36.5	0.107
	East Asia	4	1.023	0.916–1.142	0.685	0	0.988
	population-based	13	0.978	0.900-1.062	0.59	15.5	0.288
	hospital-based	2	1.114	0.931–1.334	0.238	0	0.562
rs951436	Caucasians	13	1.017	0.905–1.144	0.772	48.2	0.026
	East Asia	3	0.811	0.666–0.987	0.036	40	0.189
	population-based	14	0.997	0.892–1.114	0.955	52.1	0.012
	hospital-based	2	0.789	0.643–0.968	0.023	0	0.547
rs951439	Caucasians	10	1	0.875–1.142	0.999	28.3	0.184
	East Asia	4	1.084	0.954–1.233	0.216	0	0.898
	population-based	12	1.013	0.919–1.116	0.796	11.2	0.335
	hospital-based	2	1.164	0.937–1.445	0.17	0	0.625
rs2661319	Caucasians	12	1.059	0.965–1.162	0.229	10.4	0.343
	East Asia	3	1.13	1.009–1.266	0.035	0	0.906
	population-based	13	1.073	0.997–1.155	0.061	1.9	0.427
	hospital-based	2	1.192	0.974–1.458	0.089	0	0.838
rs10759	Caucasians	3	1.132	0.928–1.380	0.221	0	0.917
	East Asia	1	1.482	1.092–2.011	0.012	-	-

3.2.2 There was an association between rs951436 and the risk of schizophrenia in the East Asian and hospital-based subgroup analyses

Pooled and subgroup analyses of 8,990 cases and 10,568 controls were performed (Table 5). No association was found between rs951436 and the risk of schizophrenia (P_z = 0.51, OR = 0.965, 95%CI = 0.870 − 1.072) using the recessive model (Fig. 3). An association was detected in the East Asian (P_z = 0.036, OR = 0.811, 95%CI = 0.666 − 0.987) and hospital-based (P_z = 0.023, OR = 0.789, 95%CI = 0.643 − 0.968) subgroup analyses. Significant heterogeneity was observed in the pooled analysis (P_h = 0.007, I_2 = 52.5%).

Table 5
Genotype distribution and allele frequency of rs951436

Author	Year	Genotype distribution							Allele frequency			
		Cases, n			Controls, n				Cases, %		Controls, %	
		TT	TG	GG	TT	TG	GG	P_{HWE}	T	G	T	G
Jönsson	2012	223	416	197	349	711	352	0.790	862	810	1409	1415
So	2008	88	201	85	106	178	73	0.913	377	371	390	324
Guo	2006	65	141	71	88	125	67	0.088	283	271	259	301
Kampman	2006	47	114	58	90	190	109	0.682	155	169	370	408
Rizig	2006	92	202	112	99	214	116	0.987	386	426	412	446
Zhang	2005	151	290	139	137	309	174	0.993	592	568	583	657
Sobell	2005	128	300	140	179	340	170	0.735	556	580	698	680
Cordeiro	2005	86	142	40	188	299	83	0.040	314	222	675	465
Prasad	2005	15	11	4	9	11	7	0.348	41	19	29	25
Morris	2004	54	124	71	64	115	52	0.980	232	266	243	219
Williams	2004	180	342	161	146	340	189	0.765	702	664	632	718
Betcheva	2009	55	113	87	136	277	139	0.932	388	287	549	555
Chowdari	2002	39	75	35	38	59	30	0.449	153	145	135	119
Sanders	2008	458	935	477	527	1000	475	0.988	1851	1889	2054	1950
Wood	2007	101	137	72	68	148	74	0.719	339	281	284	296
Ishiguro	2006	529	978	409	566	932	420	0.325	2036	1796	2064	1772

3.2.3 There was no association between rs951439 and the risk of schizophrenia

To evaluate the relationship between rs951439 and the risk of schizophrenia, 7,995 cases and 8,646 controls were included in the pooled and subgroup analyses (Table 6). Detailed genotype frequencies were not available in [43]; thus,

these data were only included in the allele contrast. No relationship between rs951439 and the risk of schizophrenia was detected in the pooled analysis (P_z = 0.414, OR = 1.036, 95%CI = 0.952 − 1.128) using the dominant model (Fig. 4) or in the subgroup analyses by ethnicity and control source. No significant heterogeneity was observed in the pooled or subgroup analyses.

Table 6
Genotype distribution and allele frequency of rs951439

Author	Year	Genotype distribution							Allele frequency			
		Cases, n			Controls, n				Cases, %		Controls, %	
		AA	AG	GG	AA	AG	GG	P_{HWE}	A	G	A	G
So	2008	84	206	125	112	254	148	0.877	374	456	478	550
Guo	2006	49	145	92	56	143	83	0.692	243	329	255	309
Rizig	2006	66	196	147	70	206	153	0.962	328	490	346	512
Zhang	2005	112	286	182	90	292	238	0.977	510	650	472	768
Sobell	2005	90	273	205	129	335	225	0.827	453	683	593	785
Cordeiro	2005	44	136	83	97	292	172	0.156	224	302	486	636
Prasad	2005	10	13	7	7	7	13	0.018	33	27	21	33
Morris	2004	38	119	92	49	115	67	0.979	195	303	213	249
Williams	2004	111	344	231	104	333	250	0.689	566	806	541	833
Betcheva	2009	39	92	54	29	88	66	0.970	170	200	146	220
Chowdari	2002	29	74	46	26	62	39	0.881	132	166	114	140
Sanders	2008	313	904	653	355	976	671	0.998	1530	2210	1686	2318
Ishiguro	2006	342	956	621	364	967	573	0.219	1640	2198	1695	2113
Yue	2007	76	195	115	75	183	132	0.418	347	425	333	447
Qian	2005	-	-	-	-	-	-	-	498	598	613	493

3.2.4. Rs2661319 might be a risk factor for schizophrenia

Pooled and subgroup analyses of 8,320 cases and 9,440 controls were performed (Table 7). Of the five genetic models, significant differences were detected when using allele contrast (C vs T, P_z = 0.023), homozygous codominant (CC vs TT, P_z = 0.034), dominant (CC + CT vs TT, P_z = 0.016), and recessive (CC vs CT + TT, P_z = 0.046). According to the dominant model (Fig. 5), the genotype CC + CT might be a risk factor for schizophrenia (P_z = 0.016, OR = 1.087, 95%CI = 1.016 − 1.164). An association was detected in the East Asian subgroup analysis (P_z = 0.035, OR = 1.13, 95%CI = 1.009 − 1.266), with a power of 0.694. No significant heterogeneity was observed in the pooled or subgroup analyses.

Table 7

Genotype distribution and allele frequency of rs2661319

Author	Year	Genotype distribution							Allele frequency			
		Cases, n			Controls, n				Cases, %		Controls, %	
		CC	CT	TT	CC	CT	TT	P_{HWE}	C	T	C	T
Réthelyi	2010	59	139	82	51	115	64	0.961	257	303	217	243
So	2008	123	207	95	121	267	130	0.478	453	397	509	527
Guo	2006	68	134	79	65	130	80	0.391	270	292	260	290
Rizig	2006	120	207	89	128	214	90	0.975	447	385	470	394
Zhang	2005	157	290	134	194	306	120	0.973	604	558	694	546
Sobell	2005	155	299	114	193	335	161	0.504	609	527	721	657
Cordeiro	2005	49	139	79	89	305	176	0.022	237	297	483	657
Prasad	2005	4	10	16	7	11	9	0.348	18	42	25	29
Morris	2004	76	123	50	57	115	59	0.948	275	223	229	233
Williams	2004	277	331	165	205	329	139	0.740	885	661	739	607
Bakker	2007	62	136	75	113	286	181	0.999	262	284	510	650
Betcheva	2009	78	114	53	124	290	140	0.261	270	220	538	570
Chowdari	2002	39	73	35	30	68	29	0.424	151	143	128	126
Sanders	2008	525	932	413	515	1001	487	0.989	1982	1758	2031	1975
Ishiguro	2006	264	929	722	267	866	778	0.297	1457	2373	1400	2422

3.2.5. Genotype CC + CA of rs10759 might be a risk factor for schizophrenia

A total of 2,752 cases and 2,866 controls were analyzed in pooled and subgroup analyses (Table 8). Significant differences were observed in two of the genetic models, allele contrast (C vs A, $P_z = 0.046$) and dominant (CC + CA vs AA, $P_z = 0.016$). Using the random effects model, the dominant model was selected (Fig. 6). The genotype CC + CA of rs10759 was a risk factor for schizophrenia ($P_z = 0.016$, OR = 1.226, 95%CI = 1.038 − 1.448), with a power of 0.694. An association was found in the East Asian population ($P_z = 0.012$, OR = 1.482, 95%CI = 1.092 − 2.011). No significant heterogeneity was observed in the pooled or subgroup analyses.

Table 8

Genotype distribution and allele frequency of rs10759

Author	Year	Genotype distribution							Allele frequency			
		Cases, n			Controls, n				Cases, %		Controls, %	
		AA	AC	CC	AA	AC	CC	P_{HWE}	A	C	A	C
Betcheva	2009	13	71	101	13	73	98	0.906	97	273	99	269
Sanders	2008	165	781	924	197	862	942	0.992	1111	2629	1256	2746
Wood	2007	21	135	155	24	133	134	0.257	177	445	181	401
Yue	2007	105	190	91	139	199	52	0.144	400	372	477	303

Figure 1. Article selection process in the present meta-analysis.

Figure 2. Forest plot of the association between rs10917670 and schizophrenia using a recessive model (GG vs GA + AA).

Figure 3. Forest plot of the association between rs951436 and schizophrenia using a recessive model (TT vs TG + GG).

Figure 4. Forest plot of the association between rs951439 and schizophrenia using a dominant model (GG + GA vs AA).

Figure 5. Forest plot of the association between rs2661319 and schizophrenia using a dominant model (CC + CT vs TT).

Figure 6. Forest plot of the association between rs10759 and schizophrenia using a dominant model (CC + CA vs AA).

3.2.6. Sensitivity analysis

Sensitivity analysis was conducted by omitting each study in turn. The results showed that pooled ORs did not change significantly; thus, the results were considered stable and reasonable.

3.2.7. Publication bias

Publication bias could be visualized using funnel plots. No evidence of publication bias was found in the pooled analysis (Figures S1–S5).

5. Discussion

No association between rs10917670 and rs951439 and the risk of schizophrenia was detected in the present study, which was consistent with previous meta-analyses [17–19]. In the East Asian and hospital-based subgroup analyses, an association between the genotype TT of rs951436 and the risk of schizophrenia was found; however, this relationship was not detected in the pooled analysis. Therefore, the geographical environment, culture, lifestyle, and genetic background might affect polymorphisms [30, 34, 42]. It was studied that rs951436 was associated with magnetic resonance imaging measurements of functional activation and connectivity related to working memory, an intermediate phenotype of schizophrenia [44]. Moreover, Prasad et al. reported that rs951436 was related the volume of dorsolateral prefrontal cortex (DLPFC) [32]. But the mechanism remained unclear.

Rs2661319 and rs10759 were found to be associated with the risk of schizophrenia in the present study, which was inconsistent with previous meta-analyses. It was detected by subgroup analyses that the East Asian population contributed to this association. It was previously reported that rs2661319 was related to RGS4-1 mRNA level, which was decreased in the postmortem DLPFC of schizophrenic patients [11]. Moreover, rs2661319 was demonstrated to be associated with a more severe baseline total PANSS score and the treatment effect of perphenazine [45]. The rs10759 polymorphism was suggested to increase the risk of schizophrenia by altering the binding of miRNA-124 to its target [46]. MiRNA-124 might bind to the 3'UTR of mRNAs containing target sites, resulting in miRNA-mediated gene silencing, translational inhibition, and induction of mRNA de-adenylation or decay [47]. The level of RGS4 might be decreased, leading to dysfunction of neurotransmission.

More relevant data were included in our meta-analysis than those in previous meta-analyses, for instance, an increased number of more SNPs (5), and databases ((PubMed and SZGene, CNKI, Wanfang and Weipu). However, the results described herein should be interpreted with caution. First, in the present study, the East Asian population contributed to the association between the RGS4 gene and the risk of schizophrenia; however, the sample size was relatively small, and the power was low. Further articles are needed to form a representative and comprehensive conclusion. Second, family-based and functional studies were not included in the present meta-analysis. In addition, it was reported that there was an association between DLPFC volume and RGS4 genotype interacting with COMT rs4818[48]; thus, this association warrants further gene–gene interaction [49, 50] and functional studies.

6. Conclusion

No association between rs10917670 and rs951439 and the risk of schizophrenia was found. In the East Asian and hospital-based subgroup analyses, an association between rs951436 and the risk of schizophrenia was demonstrated. The genotypes CC + CT of rs2661319 and CC + CA of rs10759 might be risk factors for schizophrenia, and the East Asian population contributed to this association. Further updated gene–gene interaction and functional studies are needed.

7. Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

This was an evidence synthesis study; all data were available from the primary research studies or could be provided by the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

BW designed the study and wrote the protocol. FX and LL managed the literature search, which was checked by XW, YL, and XX. FX performed analyses. The manuscript was written by FX, and corrected by JY. All authors have read and approved the manuscript.

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Authors' information

[1] *School of Forensic Medicine, China Medical University.* Physical address*: School of Forensic Medicine, China Medical University. No. 77 Puhe Road, Shenbei New District, Shenyang, 110122, China.*

[2] *Department of Respiratory and Critical Care Medicine, First Hospital of China Medical University, Shenyang, Liaoning, China*

Abbreviations

DSM-IV: Diagnostic and Statistical Manual– Fourth Edition; RGS4: Regulator of G-protein signaling 4; RGS: Regulators of G-protein signaling; GPCRs: G-protein coupled receptors; DLPFC: decreased dorsolateral prefrontal cortex; OR: odds ratios; CIs: confidence intervals; 3' UTR: 3' untranslated region.

References

1. Wray NR, Visscher PM: Narrowing the boundaries of the genetic architecture of schizophrenia. Schizophr Bull 2010, 36(1):14-23. 2. Sullivan PF: The genetics of schizophrenia. PLoS Med 2005, 2(7):e212. 3. Cardno AG, Gottesman, II: Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. American journal of medical genetics 2000, 97(1):12-17. 4. Huang MW, Lin YJ, Chang CW, Lei FJ, Ho EP, Liu RS, Shyu WC, Hsieh CH: RGS4 deficit in prefrontal cortex contributes to the behaviors related to schizophrenia via system xc (-)-mediated glutamatergic dysfunction in mice. Theranostics 2018, 8(17):4781-4794. 5. De Vries L, Zheng B, Fischer T, Elenko E, Farquhar MG: The regulator of G protein signaling family. Annu Rev Pharmacol Toxicol 2000, 40:235-271. 6. Schwarz E: A gene-based review of RGS4 as a putative risk gene for psychiatric illness. Am J Med Genet B Neuropsychiatr Genet 2018, 177(2):267-273. 7. Taymans JM, Leysen JE, Langlois X: Striatal gene expression of RGS2 and RGS4 is specifically mediated by dopamine D1 and D2 receptors: clues for RGS2 and RGS4 functions. J Neurochem 2003, 84(5):1118-1127. 8. Soler J, Miret S, Lazaro L, Parellada M, Martin M, Lera-Miguel S, Rosa A, de Castro-Catala M, Cuesta MJ, Fananas L et al: Influence of DAOA and RGS4 genes on the risk for psychotic disorders and their associated executive dysfunctions: A family-based study. Eur Psychiatry 2016, 32:42-47. 9. Mirnics K, Middleton FA, Stanwood GD, Lewis DA, Levitt P: Disease-specific changes in regulator of G-protein signaling 4 (RGS4) expression in schizophrenia. Molecular psychiatry 2001, 6(3):293-301. 10. Ding L, Hegde AN: Expression of RGS4 splice variants in dorsolateral prefrontal cortex of schizophrenic and bipolar disorder patients. Biol Psychiatry 2009, 65(6):541-545. 11. Ding L, Styblo M, Drobna Z, Hegde AN: Expression of the Longest RGS4 Splice Variant in the Prefrontal Cortex Is Associated with Single Nucleotide Polymorphisms in Schizophrenia Patients. Front Psychiatry 2016, 7:26. 12.

Kampman O, Illi A, Hanninen K, Katila H, Anttila S, Rontu R, Mattila KM, Leinonen E, Lehtimaki T: RGS4 genotype is not associated with antipsychotic medication response in schizophrenia. J Neural Transm (Vienna) 2006, 113(10):1563-1568. 13. Wood LS, Pickering EH, Dechairo BM: Significant support for DAO as a schizophrenia susceptibility locus: examination of five genes putatively associated with schizophrenia. Biol Psychiatry 2007, 61(10):1195-1199. 14. Nicodemus KK, Kolachana BS, Vakkalanka R, Straub RE, Giegling I, Egan MF, Rujescu D, Weinberger DR: Evidence for statistical epistasis between catechol-O-methyltransferase (COMT) and polymorphisms in RGS4, G72 (DAOA), GRM3, and DISC1: influence on risk of schizophrenia. Hum Genet 2007, 120(6):889-906. 15. Zhang F, St Clair D, Liu X, Sun X, Sham PC, Crombie C, Ma X, Wang Q, Meng H, Deng W et al: Association analysis of the RGS4 gene in Han Chinese and Scottish populations with schizophrenia. Genes Brain Behav 2005, 4(7):444-448. 16. Mahendran R, Puthussery S, Amalan M: Prevalence of antenatal depression in South Asia: a systematic review and meta-analysis. J Epidemiol Community Health 2019, 73(8):768-777. 17. Talkowski ME, Seltman H, Bassett AS, Brzustowicz LM, Chen X, Chowdari KV, Collier DA, Cordeiro Q, Corvin AP, Deshpande SN et al: Evaluation of a susceptibility gene for schizophrenia: genotype based meta-analysis of RGS4 polymorphisms from thirteen independent samples. Biol Psychiatry 2006, 60(2):152-162. 18. Guo S, Tang W, Shi Y, Huang K, Xi Z, Xu Y, Feng G, He L: RGS4 polymorphisms and risk of schizophrenia: an association study in Han Chinese plus meta-analysis. Neurosci Lett 2006, 406(1-2):122-127. 19. Li D, He L: Association study of the G-protein signaling 4 (RGS4) and proline dehydrogenase (PRODH) genes with schizophrenia: a meta-analysis. Eur J Hum Genet 2006, 14(10):1130-1135. 20. Ayano G, Tesfaw G, Shumet S: The prevalence of schizophrenia and other psychotic disorders among homeless people: a systematic review and meta-analysis. BMC Psychiatry 2019, 19(1):370. 21. Xu FL, Wang BJ, Yao J: Association between the SLC6A4 gene and schizophrenia: an updated meta-analysis. Neuropsychiatr Dis Treat 2019, 15:143-155. 22. Wang CW, Ma M, Lu WG, Luo RQ: Association between prodynorphin gene polymorphisms and opioid dependence susceptibility: a meta-analysis. BMC Psychiatry 2019, 19(1):281. 23. Xu FL, Ding M, Wu X, Liu YP, Xia X, Yao J, Wang BJ: A Meta-analysis of the Association Between SLC6A3 Gene Polymorphisms and Schizophrenia. J Mol Neurosci 2019. 24. Naing C, Reid SA, Aung K: Comparing antibiotic treatment for leptospirosis using network meta-analysis: a tutorial. BMC Infect Dis 2017, 17(1):29. 25. Du T, Chen K, Zheng S, Bao M, Huang Y, Wu K: Association Between Alcohol Consumption and Risk of Nasopharyngeal Carcinoma: A Comprehensive Meta-Analysis of Epidemiological Studies. Alcohol Clin Exp Res 2019, 43(11):2262-2273. 26. Xu FL, Wu X, Zhang JJ, Wang BJ, Yao J: A meta-analysis of data associating DRD4 gene polymorphisms with schizophrenia. Neuropsychiatr Dis Treat 2018, 14:153-164. 27. Chowdari KV, Bamne M, Wood J, Talkowski ME, Mirnics K, Levitt P, Lewis DA, Nimgaonkar VL: Linkage disequilibrium patterns and functional analysis of RGS4 polymorphisms in relation to schizophrenia. Schizophr Bull 2008, 34(1):118-126. 28. So HC, Chen RY, Chen EY, Cheung EF, Li T, Sham PC: An association study of RGS4 polymorphisms with clinical phenotypes of schizophrenia in a Chinese population. Am J Med Genet B Neuropsychiatr Genet 2008, 147B(1):77-85. 29. Rethelyi JM, Bakker SC, Polgar P, Czobor P, Strengman E, Pasztor PI, Kahn RS, Bitter I: Association study of NRG1, DTNBP1, RGS4, G72/G30, and PIP5K2A with schizophrenia and symptom severity in a Hungarian sample. Am J Med Genet B Neuropsychiatr Genet 2010, 153B(3):792-801. 30. Sobell JL, Richard C, Wirshing DA, Heston LL: Failure to confirm association between RGS4 haplotypes and schizophrenia in Caucasians. Am J Med Genet B Neuropsychiatr Genet 2005, 139B(1):23-27. 31. Cordeiro Q, Talkowski ME, Chowdari KV, Wood J, Nimgaonkar V, Vallada H: Association and linkage analysis of RGS4 polymorphisms with schizophrenia and bipolar disorder in Brazil. Genes Brain Behav 2005, 4(1):45-50. 32. Prasad KM, Chowdari KV, Nimgaonkar VL, Talkowski ME, Lewis DA, Keshavan MS: Genetic polymorphisms of the RGS4 and dorsolateral prefrontal cortex morphometry among first episode schizophrenia patients. Mol Psychiatry 2005, 10(2):213-219. 33. Morris DW, Rodgers A, McGhee KA, Schwaiger S, Scully P, Quinn J, Meagher D, Waddington JL, Gill M, Corvin AP: Confirming RGS4 as a susceptibility gene for schizophrenia. Am J Med Genet B Neuropsychiatr Genet 2004, 125B(1):50-53. 34. Williams NM, Preece A, Spurlock G, Norton N, Williams HJ, McCreadie RG, Buckland P, Sharkey V, Chowdari KV, Zammit S et al: Support for RGS4 as a susceptibility gene for schizophrenia. Biol Psychiatry 2004, 55(2):192-195. 35. Bakker SC, Hoogendoorn ML, Hendriks J, Verzijlbergen K, Caron S, Verduijn W, Selten JP,

Pearson PL, Kahn RS, Sinke RJ: The PIP5K2A and RGS4 genes are differentially associated with deficit and non-deficit schizophrenia. Genes Brain Behav 2007, 6(2):113-119. 36. Betcheva ET, Mushiroda T, Takahashi A, Kubo M, Karachanak SK, Zaharieva IT, Vazharova RV, Dimova, II, Milanova VK, Tolev T et al: 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 2009, 54(2):98-107. 37. Chowdari KV, Mirnics K, Semwal P, Wood J, Lawrence E, Bhatia T, Deshpande SN, B KT, Ferrell RE, Middleton FA et al: Association and linkage analyses of RGS4 polymorphisms in schizophrenia. Hum Mol Genet 2002, 11(12):1373-1380. 38. Sanders AR, Duan J, Levinson DF, Shi J, He D, Hou C, Burrell GJ, Rice JP, Nertney DA, Olincy A et al: No significant association of 14 candidate genes with schizophrenia in a large European ancestry sample: implications for psychiatric genetics. Am J Psychiatry 2008, 165(4):497-506. 39. Ishiguro H, Horiuchi Y, Koga M, Inada T, Iwata N, Ozaki N, Ujike H, Muratake T, Someya T, Arinami T: RGS4 is not a susceptibility gene for schizophrenia in Japanese: association study in a large case-control population. Schizophr Res 2007, 89(1-3):161-164. 40. Wei-hua Yue H-dZ, Fu-lei Zhang, Mei Qu, Shui-hua Han, Da-rong Zhang, Yan Ruan, Tian-lan Lu, Dai Zhang: Association study of the regulator of G -protein signaling 4(RGS4) polymorphisms with schizophrenia. Chinese Mental Health Journal 2007, 21(3):181-185. 41. Jonsson EG, Saetre P, Nyholm H, Djurovic S, Melle I, Andreassen OA, Skjodt C, Thygesen JH, Werge T, Hall H et al: Lack of association between the regulator of G-protein signaling 4 (RGS4) rs951436 polymorphism and schizophrenia. Psychiatr Genet 2012, 22(5):263-264. 42. Rizig MA, McQuillin A, Puri V, Choudhury K, Datta S, Thirumalai S, Lawrence J, Quested D, Pimm J, Bass N et al: Failure to confirm genetic association between schizophrenia and markers on chromosome 1q23.3 in the region of the gene encoding the regulator of G-protein signaling 4 protein (RGS4). Am J Med Genet B Neuropsychiatr Genet 2006, 141B(3):296-300. 43. Xue-qing Qian LH: Locus mapping and mutation detecting for Blepharophimosis ptosis epicanthus inversus syndrome(BPES) and a study of the candidate gene to schizophrenia 2005. 44. Meyer-Lindenberg A, Weinberger DR: Intermediate phenotypes and genetic mechanisms of psychiatric disorders. Nat Rev Neurosci 2006, 7(10):818-827. 45. Campbell DB, Ebert PJ, Skelly T, Stroup TS, Lieberman J, Levitt P, Sullivan PF: Ethnic stratification of the association of RGS4 variants with antipsychotic treatment response in schizophrenia. Biol Psychiatry 2008, 63(1):32-41. 46. Gong Y, Wu CN, Xu J, Feng G, Xing QH, Fu W, Li C, He L, Zhao XZ: Polymorphisms in microRNA target sites influence susceptibility to schizophrenia by altering the binding of miRNAs to their targets. Eur Neuropsychopharmacol 2013, 23(10):1182-1189. 47. Djuranovic S, Nahvi A, Green R: miRNA-mediated gene silencing by translational repression followed by mRNA deadenylation and decay. Science 2012, 336(6078):237-240. 48. Lener MS, Goodnow SJ, Wood JA, Chowdari KV, Keshavan MS, Nimgaonkar V, Prasad KM: RGS4 and COMT risk variants are associated with brain structural alterations. Schizophr Res 2013, 150(1):321-322. 49. Zeng D, He S, Yu S, Li G, Ma C, Wen Y, Shen Y, Yu Y, Li H: Analysis of the association of MIR124-1 and its target gene RGS4 polymorphisms with major depressive disorder and antidepressant response. Neuropsychiatr Dis Treat 2018, 14:715-723. 50. Lipska BK, Mitkus S, Caruso M, Hyde TM, Chen J, Vakkalanka R, Straub RE, Weinberger DR, Kleinman JE: RGS4 mRNA expression in postmortem human cortex is associated with COMT Val158Met genotype and COMT enzyme activity. Hum Mol Genet 2006, 15(18):2804-2812.

Figures

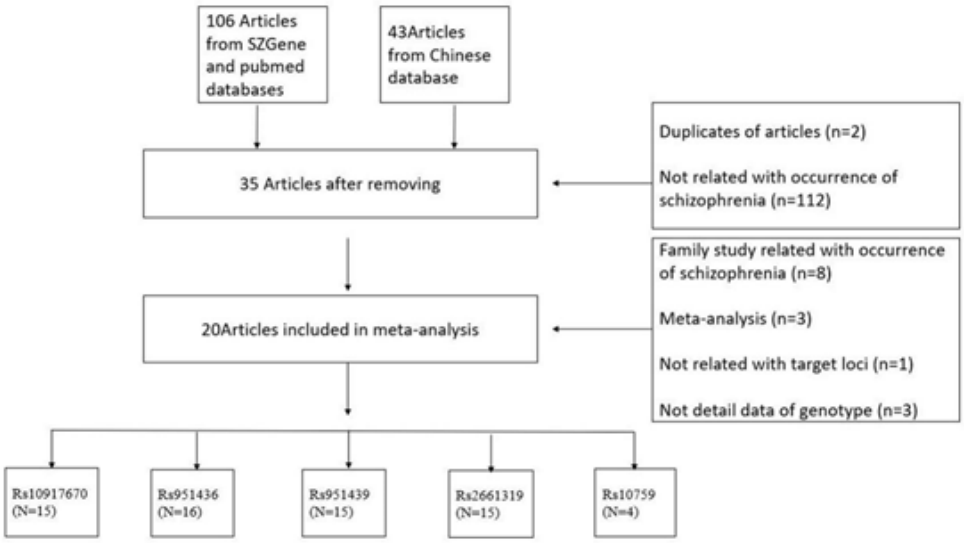

Figure 1

Article selection process in this meta-analysis.

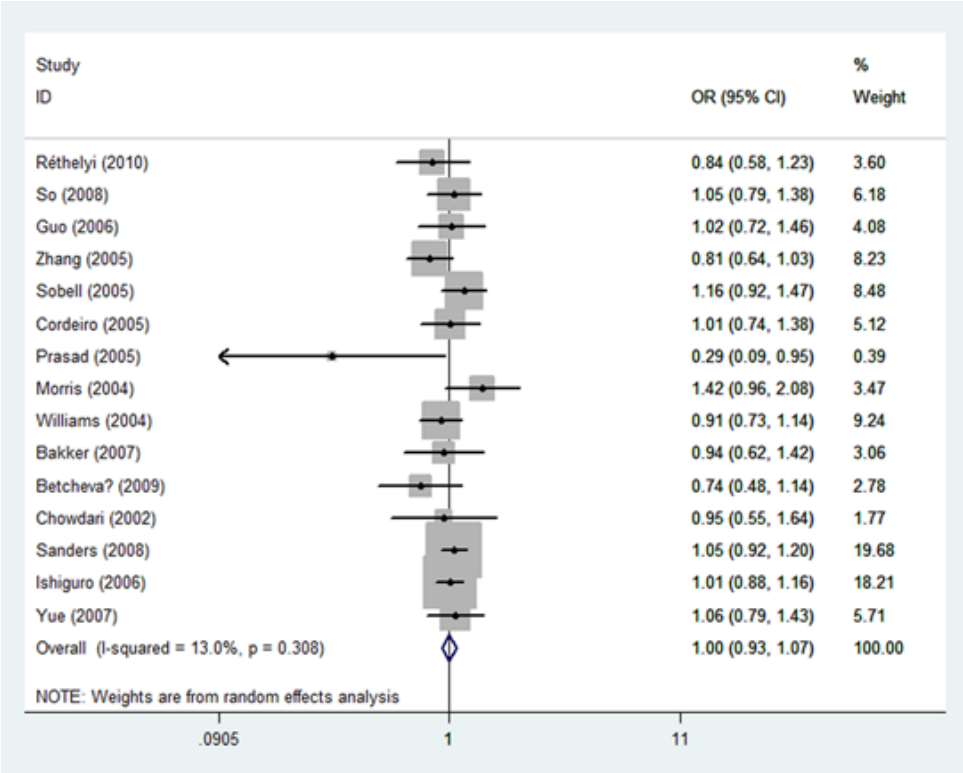

Figure 2

Forest plot of the association between of rs10917670 and schizophrenia in recessive model (GG vs GA+AA).

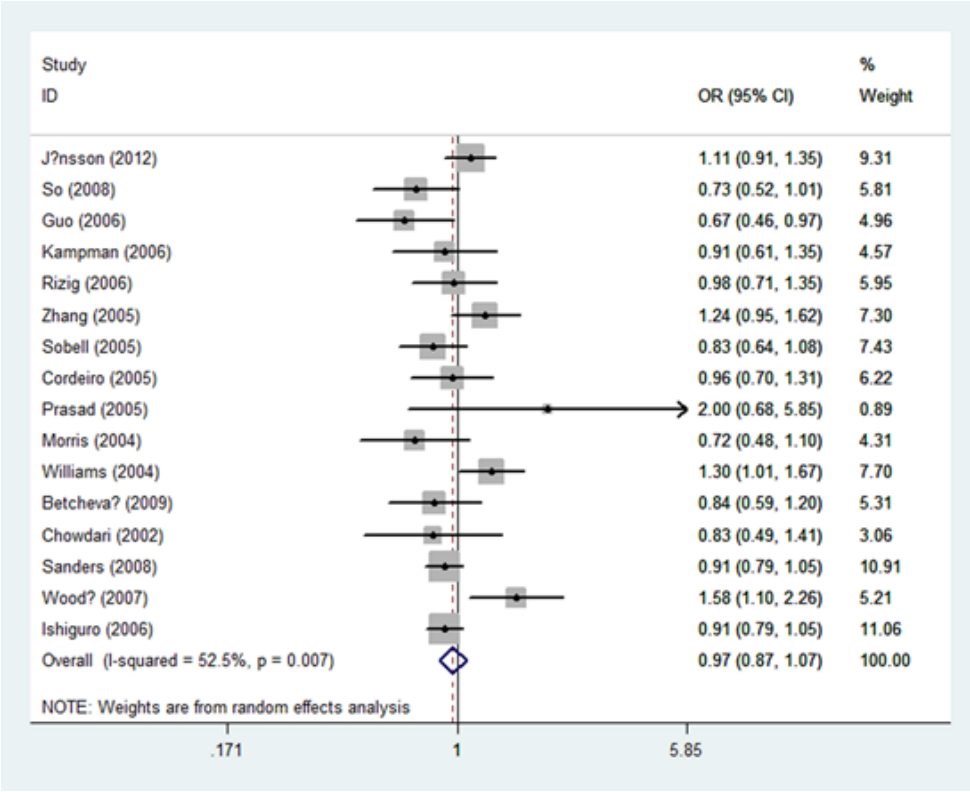

Figure 3

Forest plot of the association between of rs951436 and schizophrenia in recessive model (TT vs TG+GG).

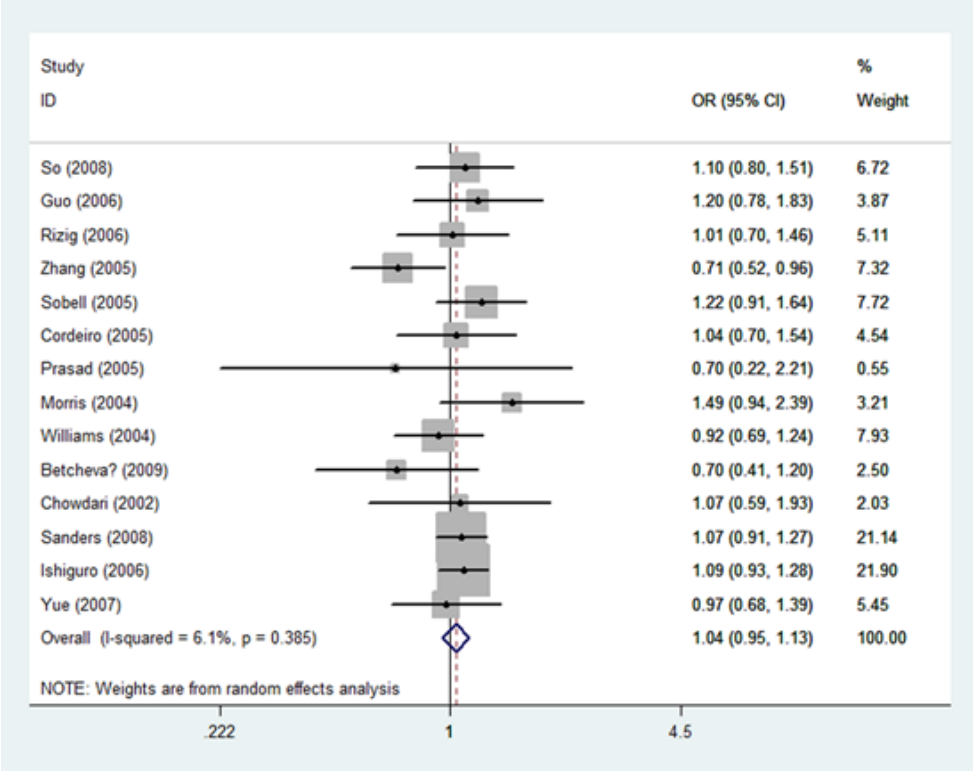

Figure 4

Forest plot of the association between of rs951439 and schizophrenia in dominant model (GG+GA vs AA).

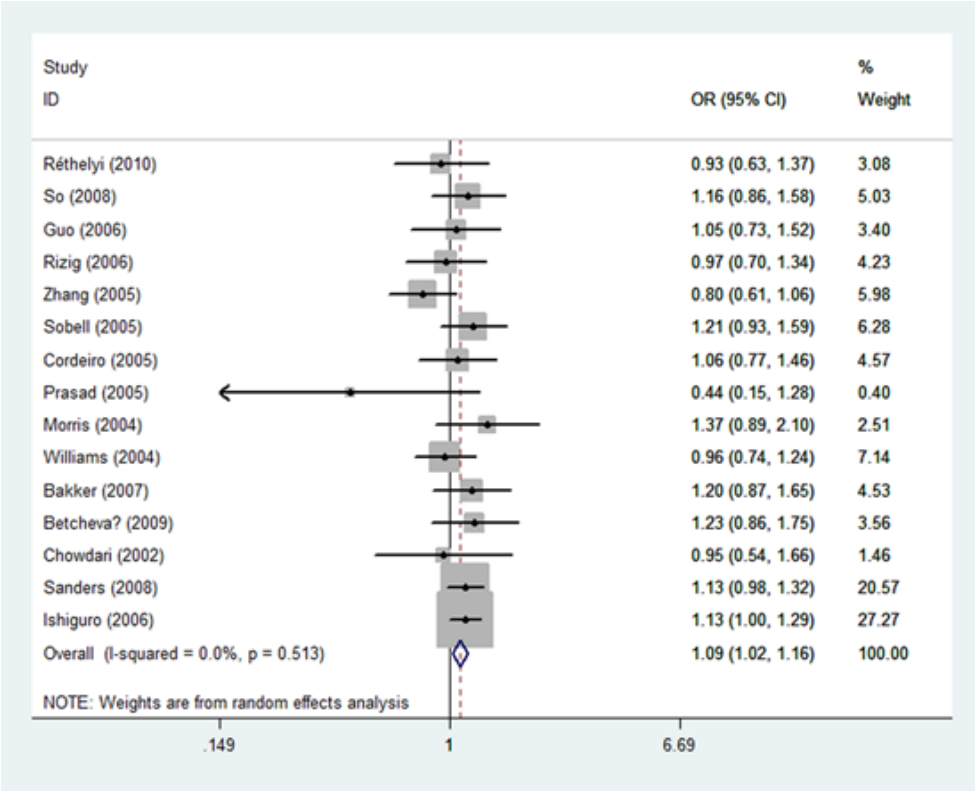

Figure 5

Forest plot of the association between of rs2661319 and schizophrenia in dominant model (CC+CT vs TT).

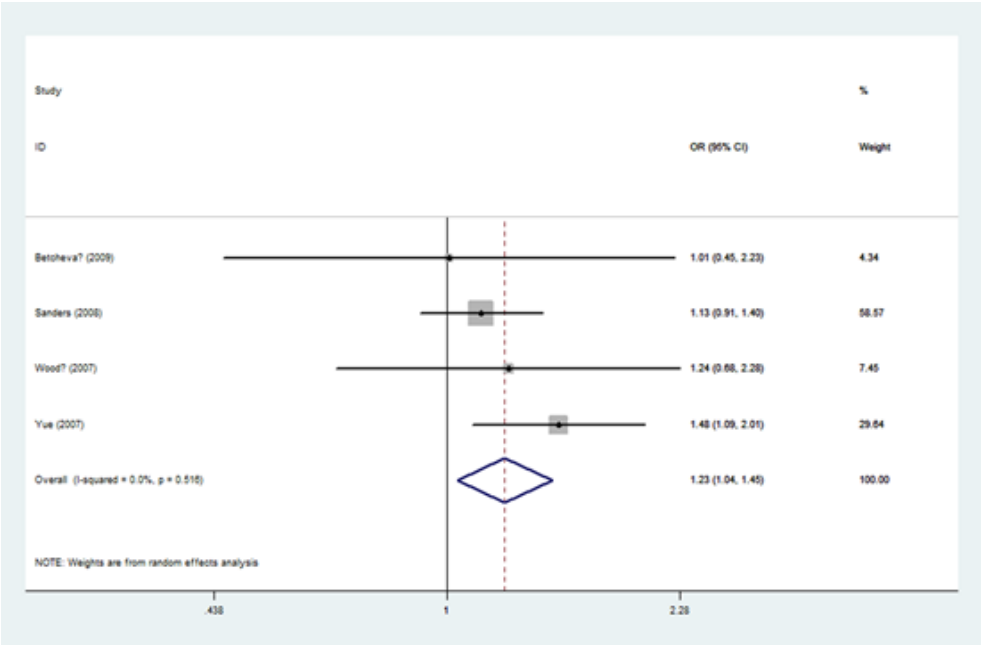

Figure 6

Forest plot of the association between of rs10759 and schizophrenia in dominant model (CC+CA vs AA).

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