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The Correlation Between Vitamin D Receptor (*VDR*) Gene Polymorphisms and Autism: A Meta-analysis

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Abstract

Vitamin D receptor (*VDR*) polymorphisms are risk factors for autism. We performed a systematic meta-analysis to explore the relationship between *VDR* gene polymorphisms and autism. A literature review of articles from Pubmed, Embase, the Cochrane Library, and Springer was conducted up to January 28, 2019. The association between SNPs and autism was calculated using pooled odd ratios (ORs) and 95% confidence intervals (CIs). Additionally, tests for heterogeneity, publication bias, and sensitivity were conducted. Six eligible studies with a total of 2001 participants (1045 cases and 956 controls) were included. Meta-analysis indicated that the "C" allele of the rs731236 gene, including C vs. T (OR = 1.3254, 95% CI = 1.0897–1.6122), CC vs. TT (OR = 2.0871, 95% CI = 1.3395–3.2519), and CC vs. TT + CT (OR = 1.9610, 95% CI = 1.2985–2.9615), might be a risk factor for autism. Moreover, the "G" allele of rs7975232 (G vs. T: OR = 0.8228, 95% CI = 0.6814–0.9934) was associated with a protective effect against the development of autism. No significant differences were found in the allele frequencies of rs11568820, rs1544410, and rs2228570 in the cases and controls. This meta-analysis revealed that both *VDR* rs731236 and rs7975232 were significantly associated with autism, whereas *VDR* rs11568820, rs1544410, and rs2228570 might not be correlated with the incidence of autism.

Keywords Meta-analysis · Autism · Vitamin D receptor · Gene polymorphism

Introduction

Autism is an onset neurodevelopmental disorder characterized by disruption of early social interactions (Volkmar 2011). The symptoms of autism often develop gradually, and parents usually notice problems when their children are 2 or 3 years old (Crane et al. 2016). The prenatal environment, including maternal infection, maternal use of medication, and exposure to various substances (alcohol, smoking) during pregnancy, is recognized as a potential risk factor for autism (Ornoy et al. 2015). Autism impacts brain information processing by changing the connections between the organizations of nerve cells and synapses (Ozonoff et al. 2010; Minshew and Goldstein 2015). Although early behavioral and verbal interventions can improve the symptoms of autism, there is currently no effective treatment for the disease (Reichow and Wolery 2009). Thus, it is necessary to explore the pathogenesis of autism.

Recently, the relationship between autism spectrum disorder (ASD) and vitamin D has been established. It was found that vitamin D mediates the biosynthesis of neurotrophic factors and neurotransmitters, and its deficiency triggers the development of ASD (Saad et al. 2016; Máčová et al. 2017). Therefore, any change in the genes involved in the transport or binding of vitamin D could be an underlying risk factor for autism. Notably, Vitamin D exerts its effects on genes through the Vitamin D receptor (*VDR*), which may be associated with the risk of autism (Cannell and Grant 2013). The *VDR* gene is located on human chromosome 12q13.1, and several *VDR* polymorphisms can affect gene expression, including rs1544410 (BsmI), rs11568820 (Cdx2), rs2228570 (FokI), rs731236 (TaqI), and rs7975232 (Apa1) (Taymans et al. 2010). Smolders and colleagues demonstrated that these genotypes could regulate the stability of *VDR* (Smolders et al. 2009). In addition, vitamin D responsive elements (VDREs)

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can control the level of tryptophan hydroxylase (TPH) 2 and may be correlated with psychiatric disorders including autism (Kaneko et al. 2015). Despite the substantial evidence (Coşkun et al. 2016; Altun et al. 2018) regarding the potential role of *VDR* in the pathogenesis of autism, the association between *VDR* polymorphisms and autism is still inconclusive. Therefore, a detailed study is needed to draw an objective conclusion on the relationship between *VDR* gene polymorphisms and autism.

This meta-analysis was performed to identify the associations between multiple *VDR* polymorphisms (rs1544410, rs11568820, rs2228570, rs731236, and rs7975232) and the risk of autism and provide evidence for the diagnosis and treatment of autism.

Methods

Search Strategy

To identify studies that shed light on the relationship between *VDR* polymorphisms and autism risk, we conducted a systematic literature search for articles published up to January 28, 2019, in Cochrane Library (http://www.cochranelibrary.com/), Embase (http://www.embase.com), Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/), and Springer (https://link.springer.com/) database. The search terms were "autism" or "autistic", and "*VDR*" or "vitamin D receptor", and "polymorphic*" or "genetic" or "variant" or "gene". No language limitation was imposed.

Inclusion and Exclusion Criteria

All included studies were satisfied the following criteria: (1) reported the distribution of *VDR* gene mutation frequencies, including rs11568820, rs1544410, rs2228570, rs731236, and rs7975232 in autism and non-autism patients; (2) provided data on the accurate genotype or allele frequency; and (3) the research design was a case-control study. Studies meeting the following criteria were excluded: (1) insufficient data for statistical analysis; (2) the article was a letter, review, or comment; and (3) for duplicated publication or when the same population data were used for multiple studies, only the last study or the study with the most complete data were retained, and others were excluded.

Data Extraction

Two investigators independently extracted appropriate data from the eligible publications, including the first author, research area, publication year, research year, the diagnostic criteria for autism, the detection methods for genetic polymorphisms, the source of the control group, the number of subjects in the case and control groups, the sex ratio, age, and distribution of mutation frequencies of the *VDR* gene (including rs11568820, rs1544410, rs2228570, rs731236, and rs7975232). Additionally, the methodological quality of the eligible studies was assessed using the Newcastle-Ottawa Scale (NOS) (Luchini et al. 2017). Disagreements between the two investigators during data extracting were solved by discussion with the third investigator.

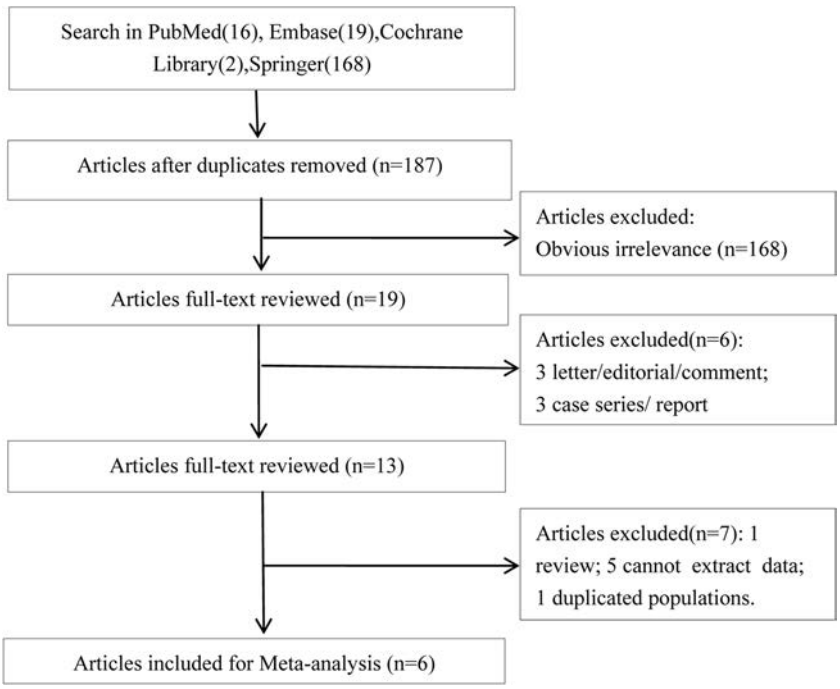

Fig. 1 Flowchart of the search strategy

Statistical Analysis

All the meta-analysis was performed using R version 3.12 (Omez et al. 2010) and odds ratio (OR) and 95% confidence intervals (CIs) were selected as the effect indicators. The allelic frequencies of variants among controls for each study were evaluated for Hardy-Weinberg equilibrium (HWE) by means of the chi-square test (Rodriguez et al. 2009). The heterogeneity was calculated using the chi-square-based Q test (Lau et al. 1997) and I^2 statistics. Briefly, $P < 0.05$ and $I^2 > 50\%$ were considered to be significant heterogeneity, and the random effect model was applied to estimate the combined effect value; otherwise, the fixed effect model was selected to calculate the merged data ($P > 0.05$ and $I^2 < 50\%$) (Ren-Nan et al. 2011). Egger's test was used to assess publication bias (Peters et al. 2006), and $P > 0.05$ indicated that no publication bias existed. Additionally, sensitivity analysis was conducted by ignoring each study to examine the stability of the results.

Results

Eligible Studies and Study Characteristics

The process and results of the literature search are presented in Fig. 1. A total of 205 studies were obtained after the preliminary search. Eighteen repetitive studies were filtered out. Of the remaining 187, 168 were excluded due to nonconformity with the objective. Following this, 13 papers (3 letter/editorial/comment; 3 case series/reports; 1 review; 5 could not extract data; and 1 duplicate population) were excluded. The remaining 6 eligible studies were included in this meta-analysis (Schmidt et al. 2015; Coşkun et al. 2016; Cieślińska et al. 2017; Balta et al. 2018; Sevcan Tug Bozdogan et al. 2018; Zhang et al. 2018).

The publication years of included studies ranged from 2015 to 2018. Three studies were conducted in Turkey, and the remaining three studies were performed in the United States, Poland, and China, respectively. A total of 2001 subjects were enrolled, including 1045 cases and 956 controls. The single nucleotide polymorphisms (SNPs) were detected using real-time polymerase chain reaction (RT-PCR) and polymerase chain reaction-fluorescence resonance energy transfer (PCR-FRET). In addition, the diagnostic criteria included the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V and DSM-IV. The general characteristics of each study are showed in Table 1. The gene distributions of rs11568820, rs1544410, rs2228570, rs731236, and rs7975232 from each study are listed in Table 2.

The NOS scores of the enrolled studies ranged from 7 to 9, indicating that they were high-quality studies (Table 1). Additionally, the distribution of genotype all conformed to HWE, except for 4 SNPs in the controls (rs7975232 in the

Table 1 The characteristics of the included studies

Author	Publication year	Location	Study year	Genotyping method	Diagnostic criteria for ASD	Characteristics of the controls	Score*	Case			Control		
								N	M/F	Age (years)	N	M/F	Age (years)
Balta B	2018	Turkey	NA	RT-PCR	DSM-IV	Healthy	9	30	26/4	Mean: 7.1	30	26/4	Mean: 7.5
Bozdogan ST	2017	Turkey	2015 .1–2017.1	RT-PCR	DSM-V	Healthy	9	85	72/13	7.38 ± 4.01	52	39/13	7.46 ± 3.87
Cieslinska A	2017	Poland	NA	PCR-RFLP	ICD-10 as ICD-F84.0	Non-ASD	7	108	91/17	6.8(3–11)	196	98/98	8.5(4–18)
Coskun S	2016	Turkey	2013.6–2015.12	RT-PCR	DSM-V	Healthy	9	237	195/42	51.1 ± 33.8 m	243	205/38	49.1 ± 17.2 m
Schmidt RJ	2015	USA	2003–2009	TaqMan	1	TD	7	384	NA	NA	234	NA	NA
Zhang ZY	2018	China	2012.9–2016.6	TaqManRT-PCR	NA	Healthy	7	201	NA	NA	201	NA	NA

ASD autism spectrum disorder; *TD* Typical development; *m* months; * NOS score (The Newcastle-Ottawa Scale); *M/F* Male/Female; *PCR-RFLP* polymerase chain reaction-restriction fragment length polymorphism; *RT-PCR* real-time polymerase chain reaction; *DSM* Diagnostic and Statistical Manuel of Mental Disorders; *1*, MIND Institute and other health or service providers, or self-referred from the CHARGE Study website

Table 2 The gene distributions of rs11568820, rs1544410, rs2228570, rs731236, and rs7975232 in the included studies

Author	Publication Year	SNP	Wild/ mutant	Case				Control				HWE in control	
				N	WH	HT	MH	N	WH	HT	MH	χ^2	*P*
Balta B	2018	rs11568820(Cdx2)	G/A	30	22	5	3	30	20	8	2	0.759	0.3836
Bozdogan ST	2017	rs731236 (TaqI)	T/C	85	37	35	13	52	21	28	3	2.771	0.0960
		rs2228570(FokI)	C/T	85	5	31	49	52	4	20	28	0.026	0.8713
		rs1544410(BsmI)	G/A	85	11	40	34	52	6	26	20	0.321	0.5712
		rs7975232 (Apa1)	T/G	85	2	56	27	52	0	35	17	13.380	**0.0003**
Cieslinska A	2017	rs2228570(FokI)	C/T	108	38	51	19	196	68	92	36	0.247	0.6192
		rs1544410(BsmI)	G/A	108	12	67	29	196	24	118	54	10.842	**0.0010**
		rs731236 (TaqI)	T/C	108	33	61	14	196	92	85	19	0.010	0.9214
		rs7975232 (Apa1)	T/G	108	22	73	13	196	26	119	51	10.941	**0.0009**
Coskun S	2016	rs1544410(BsmI)	G/A	237	90	94	53	243	85	121	37	0.321	0.5708
		rs731236 (TaqI)	T/C	237	106	89	42	243	113	108	22	0.281	0.5960
		rs2228570(FokI)	C/T	237	145	75	17	243	141	95	7	2.558	0.1097
		rs7975232 (Apa1)	T/G	237	84	106	47	243	75	120	48	< 0.001	1.0000
		rs11568820(Cdx2)	G/A	237	140	75	22	243	165	62	16	7.257	**0.0071**
Schmidt RJ	2015	rs1544410(BsmI)	G/A	316	144	131	41	193	93	77	23	1.255	0.2625
Zhang ZY	2018	rs11568820(Cdx2)	G/A	199	76	86	37	199	68	96	35	0.012	0.9113
		rs1544410(BsmI)	G/A	201	177	24	0	198	178	20	0	0.560	0.4542
		rs2228570(FokI)	T/C	199	53	99	47	197	40	104	53	0.721	0.3959

HWE Hardy-Weinberg equilibrium. $P < 0.05$ is considered representative of a departure from HWE; *SNP* single nucleotide polymorphism; *WH* wild homozygote; *HT* heterozygote; *MH* mutational homozygote. The bold sections indicate $P < 0.05$

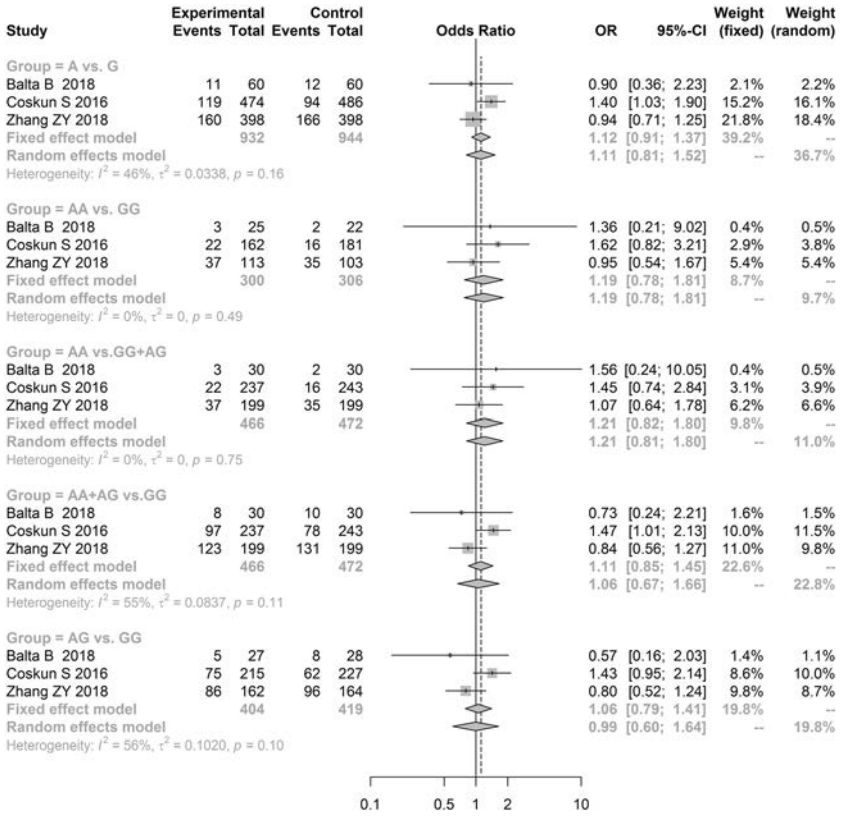

Fig. 2 Forest plots from the meta-analysis of the relationship between *VDR* rs11568820 and autism risk. Each line represents an individual study. The black dot indicates the pooled OR and 95% CI

study by Bozdogan et al., rs1544410 and rs7975232 in the study by Cieslinska et al., and rs11568820 in the study by Coskun et al.).

Meta-Analysis

A meta-analysis was performed using 4 diverse genetic models to evaluate the relationship between *VDR* polymorphisms and autism risk. The genetic models included the allele genetic model (rs11568820, A vs. G; rs1544410, A vs. G; rs2228570, T vs. C; rs731236, C vs. T; rs7975232, G vs. T), the codominant genetic model (rs11568820, AG vs. GG, AA vs. GG; rs1544410, AG vs. GG, AA vs. GG; rs2228570, TC vs. CC, TT vs. CC; rs731236, CT vs. TT, CC vs. TT; rs7975232, GT vs. TT, GG vs. TT), the recessive genetic model (rs11568820, AA vs. GG + AG; rs1544410, AA vs. GG + AG; rs2228570, TT vs. CC + TC; rs731236, CC vs. TT + CT; rs7975232, GG vs. TT + GT), and the dominant genetic model (rs11568820, AA+AG vs.GG; rs1544410, AA+AG vs. GG; rs2228570, TT + TC vs. CC; rs731236, CC + CT vs. TT; rs7975232, GG + GT vs. TT).

The heterogeneity test was statistically significant ($P < 0.05$, $I^2 > 50\%$) for 3 polymorphisms under different genetic models (rs11568820, AG vs. GG, AA+AG vs. GG; rs731236, CT vs. TT, CC + CT vs. TT; rs7975232, GG vs. TT, GG vs. TT + GT). Therefore, the random effect model was used for these in the remaining meta-analyses, whereas the fixed effect model was performed for the other polymorphisms.

No statistically significant difference was observed in the rs11568820, rs1544410, and rs2228570 gene polymorphisms (Figs. 2, 3, 4 and Table 3). For *VDR* rs731236, significantly statistical differences were found under these models: C vs. T (OR = 1.3254, 95% CI = 1.0897–1.6122, Z = 2.82, $P = 0.0048$), CC vs. TT (OR = 2.0871, 95% CI = 1.3395–3.2519, Z = 3.25, $P = 0.0011$), and CC vs. TT + CT (OR = 1.9610, 95% CI = 1.2985–2.9615, Z = 3.20, $P = 0.0014$) (Fig. 5, Table 3). More remarkably, the OR values and their 95% CI were more than 1, indicating that subjects with the "C" genotype of *VDR* rs731236 probably had an increased risk of autism. For the *VDR* rs7975232, a significant difference was detected in the allele

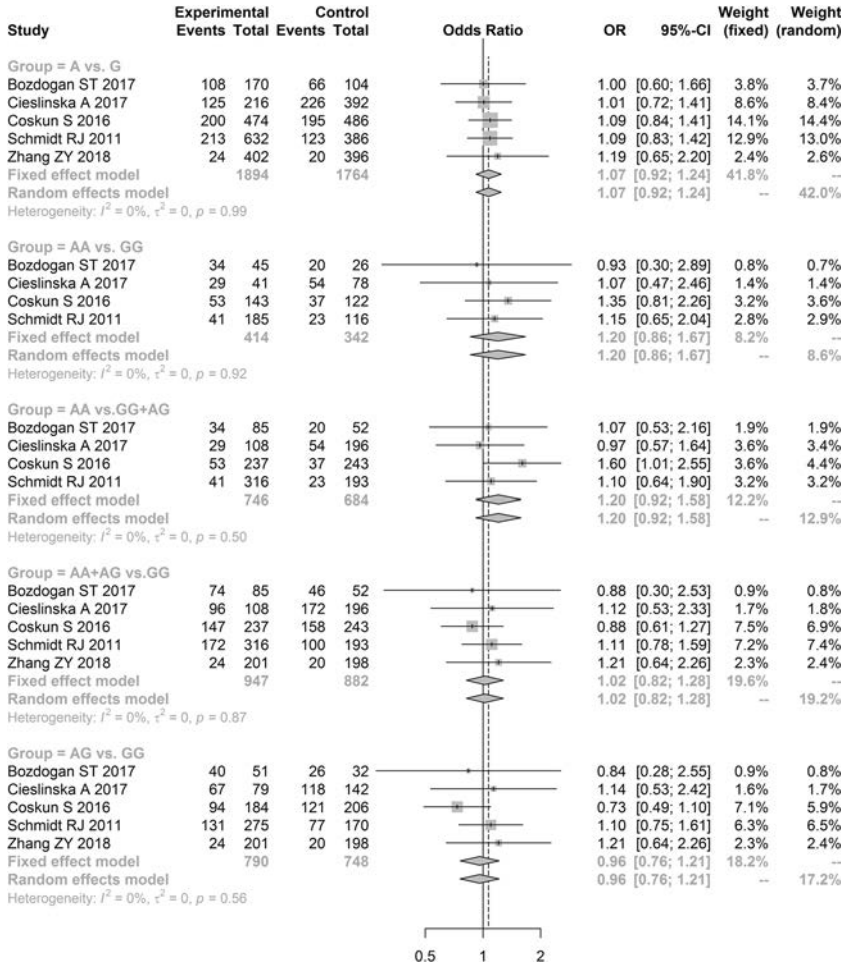

Fig. 3 Forest plots from the meta-analysis of the relationship between *VDR* rs1544410 and autism risk. Each line represents an individual study. The black dot indicates the pooled OR and 95% CI

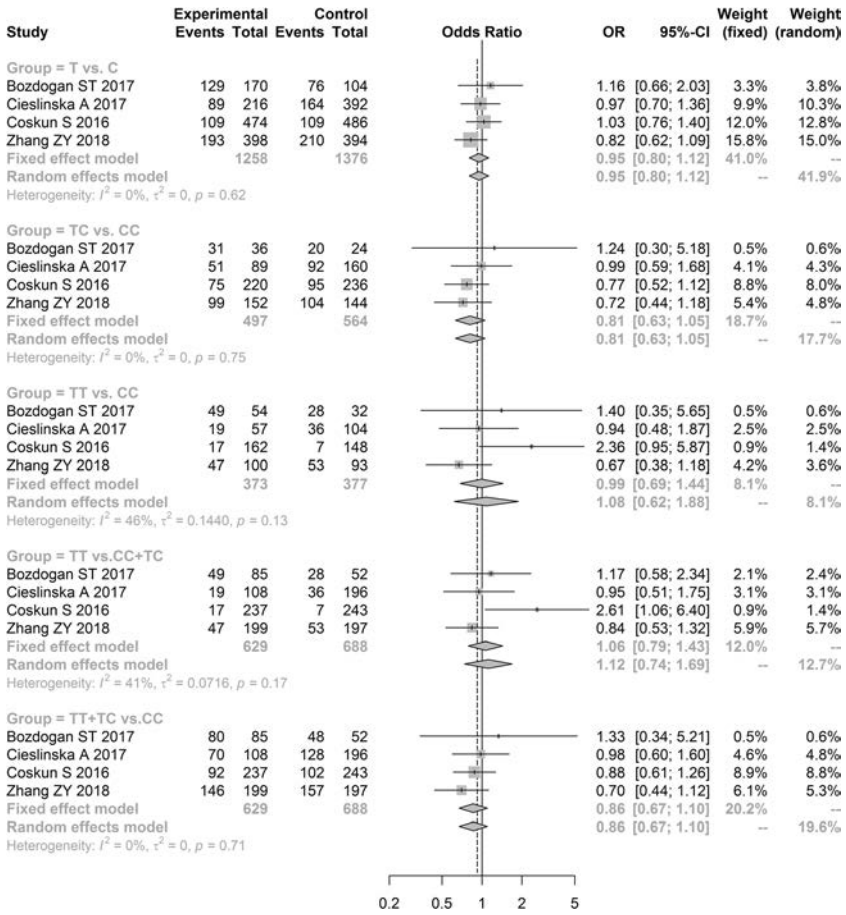

Fig. 4 Forest plots from the meta-analysis of the relationship between *VDR* rs2228570 and autism risk. Each line represents an individual study. The black dot indicates the pooled OR and 95% CI

genetic model (OR = 0.8228, 95% CI = 0.6814–0.9934, Z = 2.03, P = 0.0425) (Fig. 6, and Table 3). Notably, the OR value and 95% CI were less than 1; therefore, the "G" allele of rs7975232 might regard as a protective gene.

Sensitivity Analysis and Publication Bias

Sensitivity analysis was performed to detect the stability and reliability of the results by ignoring each study one by one. The conclusions for rs11568820, rs1544410, and rs2228570 were not reversed. However, the findings were changed for *VDR* rs731236 when excluding the study of Cieslinska et al. (Cieślińska et al. 2017) under the allele genetic model or removing the research of Coskun et al. (Coşkun et al. 2016) under the recessive genetic model. The results for rs7975232 were also reversed under the allele genetic model when the study by Cieslinska et al. (Cieślińska et al. 2017) was removed. Similarly, the outcome for the rs7975232 gene was altered under the codominant genetic model after ignoring the research of Coskun et al. (Coşkun et al. 2016). No publication bias was detected for any of the rs11568820, rs1544410, rs2228570, rs731236, or rs7975232 genetic models (Table 3).

Discussion

This meta-analysis examined the association between *VDR* polymorphisms and autism risk. A total of six studies were included. We found that the "C" allele of rs731236 was significantly associated with an increased risk of autism, while the "G" allele of rs7975232 might be a protective factor against the development of autism. However, *VDR* rs11568820, rs1544410, and rs2228570 were not connected with autism.

Cieślińska et al. claimed that the "T" allele of TaqI (*VDR* rs731236) and "A" allele of ApaI (*VDR* rs7975232) might decrease ASD incidence, by affecting the metabolism function of vitamin D3 (Cieślińska et al. 2017). Additionally, the haplotype GTTT rs2228570 of *VDR* is associated with an increased risk of ASD, and rs2228570 polymorphisms may play a role in autism by affecting the level of serum 25-hydroxyvitamin D (25(OH)D) (Coşkun et al. 2016). Unfortunately, no significant relationship was found between rs228570 and autism risk in this study; we speculated that different populations might have different ASD-related genotypes. Purportedly, the "C" allele and the "CT" genotype of rs731276 (TaqI) significantly increase the risk of ASD (Zhang et al. 2018). The child and paternal variation of TaqI (GC AA-

Table 3 Results of the meta-analysis

Gene	Gene model	Sample size			Association test			Model	Test for heterogeneity[a,b]			Egger's test[c]	
		K	Cases	Control	OR(95%CI)	Z	P		Q	P	I^2(%)	t	*P*
rs11568820	A vs. G	3	932	944	1.1157 [0.9118; 1.3653]	1.06	0.2878	Fixed	3.72	0.1555	46.3	0.1731	0.8909
	AG vs. GG	3	404	419	0.9944 [0.6036; 1.6382]	0.02	0.9824	Random	4.55	0.1029	56.0	0.6371	0.6389
	AA vs. GG	3	300	306	1.1884 [0.7789; 1.8132]	0.80	0.4234	Fixed	1.44	0.3148	0.0	0.3148	0.8058
	AA vs.GG + AG	3	466	472	1.2123 [0.8159; 1.8013]	0.95	0.3406	Fixed	0.58	0.7500	0.0	0.7140	0.6052
	AA+AG vs.GG	3	466	472	1.0567 [0.6713; 1.6634]	0.24	0.8118	Random	4.46	0.1074	55.2	0.5186	0.6954
rs1544410	A vs. G	5	1894	1764	1.0702 [0.9209; 1.2438]	0.88	0.3762	Fixed	0.33	0.9875	0.0	0.01375	0.9899
	AG vs. GG	5	790	748	0.9605 [0.7601; 1.2137]	0.34	0.7357	Fixed	2.96	0.5645	0.0	0.3747	0.7328
	AA vs. GG	4	414	342	1.1954 [0.8579; 1.6658]	1.05	0.2917	Fixed	0.49	0.9200	0.0	2.6330	0.1190
	AA vs.GG + AG	4	746	684	1.2046 [0.9194; 1.5783]	1.35	0.1769	Fixed	2.35	0.5034	0.0	1.0837	0.3918
	AA+AG vs.GG	5	947	748	1.0222 [0.8189; 1.2760]	0.19	0.8463	Fixed	1.24	0.8708	0.0	0.2457	0.8218
rs2228570	T vs. C	4	1258	1376	0.9489 [0.8029; 1.1214]	0.62	0.5383	Fixed	1.79	0.6317	0.0	1.3366	0.3131
	TC vs. CC	4	497	564	0.8145 [0.6300; 1.0530]	1.57	0.1174	Fixed	1.22	0.7492	0.0	1.1966	0.3541
	TT vs. CC	4	373	377	0.9937 [0.6855; 1.4405]	0.03	0.9734	Fixed	5.59	0.1335	46.3	1.1455	0.3706
	TT vs.CC + TC	4	629	688	1.0623 [0.7872; 1.4336]	0.40	0.6925	Fixed	5.05	0.1682	40.6	2.7705	0.1093
	TT + TC vs.CC	4	629	688	0.8590 [0.6730; 1.0964]	1.22	0.2221	Fixed	1.4	0.7062	0.0	0.7961	0.5094
rs731236	C vs. T	3	860	982	1.3254 [1.0897; 1.6122]	2.82	**0.0048**	Fixed	1.09	0.5800	0.0	0.14145	0.9105
	CT vs. TT	3	361	447	1.0980 [0.5993; 2.0116]	0.30	0.7621	Random	7.85	0.0198	74.5	0.01761	0.9888
	CC vs. TT	3	245	270	2.0871 [1.3395; 3.2519]	3.25	**0.0011**	Fixed	0.06	0.9683	0.0	3.1605	0.1951
	CC vs.TT + CT	3	430	491	1.9610 [1.2985; 2.9615]	3.20	**0.0014**	Fixed	1.35	0.5092	0.0	0.01718	0.9891
	CC + CT vs.TT	3	430	491	1.2648 [0.7929; 2.0174]	0.99	0.3241	Random	5.18	0.0751	61.4	0.03488	0.9778
rs7975232	G vs. T	3	860	982	0.8228 [0.6814; 0.9934]	2.03	**0.0425**	Fixed	2.65	0.2663	24.4	0.1026	0.9349
	GT vs. TT	3	195	217	0.7589 [0.5401; 1.0663]	1.59	0.1118	Fixed	0.36	0.8341	0.0	8.3159	0.07619
	GG vs. TT	3	430	491	0.5275 [0.2181; 1.2758]	1.42	0.1558	Random	4.79	0.0910	58.3	0.8964	0.5347
	GG vs.TT + GT	3	430	491	0.7353 [0.4043; 1.3373]	1.63	0.1039	Random	5.79	0.0553	65.5	0.2591	0.8386
	GG + GT vs.TT	3	343	375	0.7401 [0.5358; 1.0222]	1.83	0.0677	Fixed	0.98	0.6135	0.0	2.6616	0.2288

[a] Random-effects model is used when the $P < 0.05$ in the heterogeneity test; otherwise the fixed-effect model is used. [b] $P < 0.05$ is considered statistically significant for Q statistics. [c] Egger's test to evaluate publication bias, $P < 0.05$ is considered statistically significant. *OR* odds ratio; *CI* confidence interval. The bold sections indicate statistically significant differences

genotype/A-allele) are correlated with ASD, indicating that child and paternal vitamin D metabolism could be involved in the pathogenesis of ASD (Schmidt et al. 2015). Interestingly, we found that another TaqI (rs731236) with the "C" allele was related to an increased risk of autism, which was supported by Lao (Lao 2014). We observed no significant differences in the genotype and allele distributions of rs11568820 in autism patients and healthy controls. A previous study on the relationship between *VDR* polymorphisms and Alzheimer's disease (AD) found no association between AD and rs11568820 (Lee et al. 2014). Given the clinical similarities between autism and AD (disruption in language and social function), this study indirectly supports our conclusions. A prior study indicated that there was no significant difference between the allele and genotype distributions of *VDR* gene polymorphisms in ASD patients and controls (rs7975232 (Apa1), rs1544410 (Bsm1), rs2228570 (Fok1)) (Sevcan Tug Bozdogan et al. 2018). However, we found that the "G" allele of rs7975232 was associated with a decrease in autism risk. Presumably, this difference is explained by the small sample sizes and different study areas. Therefore, a larger systematic study will be required to verify the findings identified in this study.

The heterogeneity test showed statistical significance for some models of rs11568820 and rs7975232, which might be due to the following factors: (1) different regions (such as regional living habits, living environment, and economic development level, etc.) and (2) other confounding factors (including gender and age).

Some limitations of this study should be mentioned: (1) Covariate correction and subgroup analysis were not conducted due to incomplete data and the small number of included studies. These confounders might influence the results in this work to some extent. (2) Multiple mutations in the control subjects of several studies did not conform to HWE (rs7975232 in Bozdogan et al., rs1544410 and rs7975232 in Cieslinska et al.,

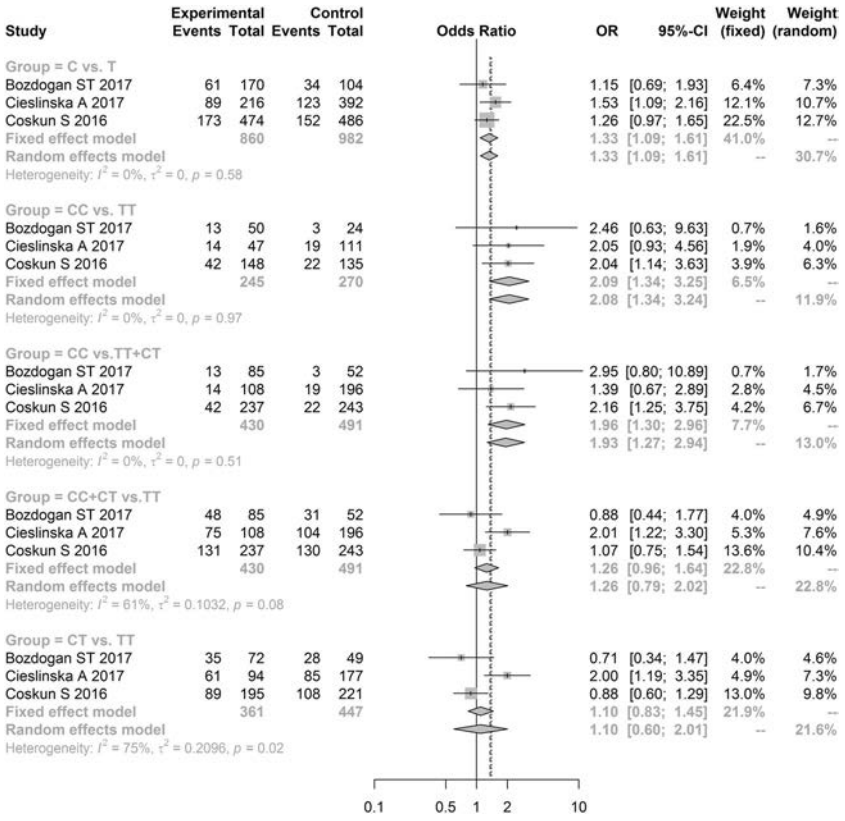

Fig. 5 Forest plots from the meta-analysis of the relationship between *VDR* rs731236 and autism risk. Each line represents an individual study. The black dot indicates the pooled OR and 95% CI

and rs11568820 in Coskun et al.). Therefore the representativeness of the population was unqualified. (3) The results of sensitivity analysis were unstable, and additional relevant articles will be needed to confirm our results. (4) A meta-analysis of

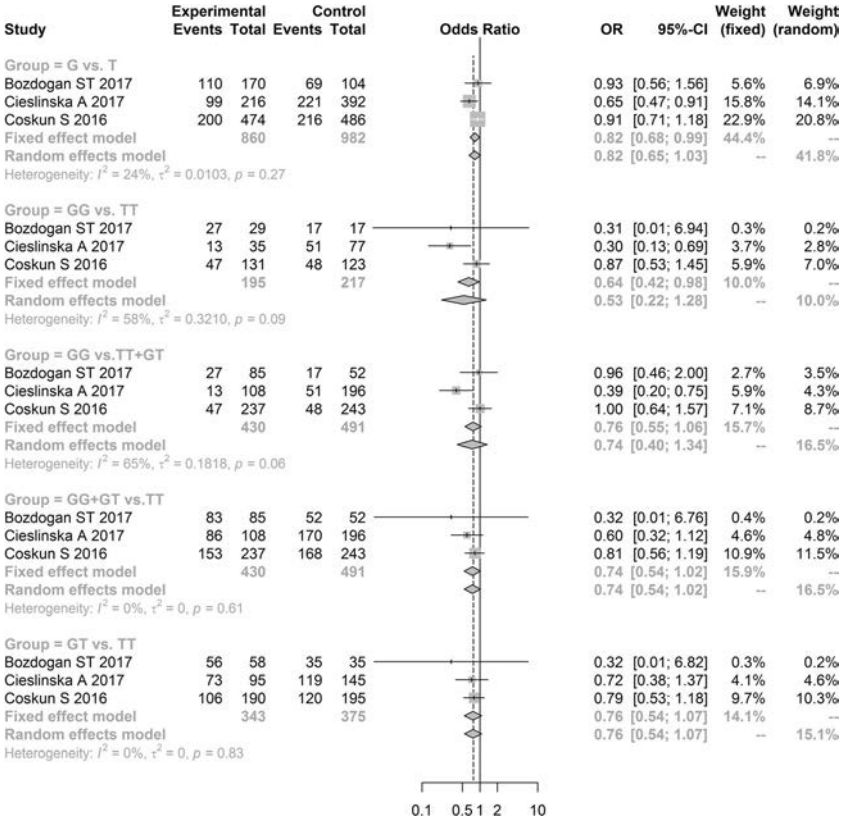

Fig. 6 Forest plots from the meta-analysis of the relationship between *VDR* rs7975232 and autism risk. Each line represents an individual study. The black dot indicates the pooled OR and 95% CI

VDR rs4516035 and *VDR* rs731276 could not be conducted due to the small number of included studies.

Conclusions

In conclusion, this comprehensive meta-analysis revealed that *VDR* rs731236 and *VDR* rs7975232 was associated with the risk of autism, while *VDR* rs11568820, rs1544410, and rs2228570 might possibly not be related to autism. However, additional validation studies, with larger sample sizes, are needed to verify our findings.

Authors' Contributions HY conceived and designed the research, acquired data, analyzed data, drafted the manuscript, and conducted the statistical analysis. XW conceived and designed the research, analyzed data, obtained funding, and revised manuscript for important intellectual content. All authors read and approved the final manuscript.

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Compliance with Ethical Standards

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Materials Not applicable.

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

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