Original Paper

Association of Dopamine Beta-Hydroxylase Polymorphisms with Alzheimer's Disease, Parkinson's Disease and Schizophrenia: Evidence Based on Currently Available Loci

Siqi Tang^{a,b} Bin Yao^{a,b} Na Li^{a,c} Shuhuang Lin^{a,b} Zunnan Huang^{a,d}

^aKey Laboratory for Medical Molecular Diagnostics of Guangdong Province, Dongguan Scientific Research Center, Guangdong Medical University, Dongguan, ^bThe Second School of Clinical Medicine, Guangdong Medical University, Dongguan, ^cSchool of Pharmacy, Guangdong Medical University, Dongguan, ^dInstitute of Marine Biomedical Research, Guangdong Medical University, Zhanjiang, China

Key Words

Dopamine beta-hydroxylase • Alzheimer's disease • Parkinson's disease • Schizophrenia • Neurodegenerative diseases • Polymorphism • Meta-analysis

Abstract

Background/Aims: The neuropathies Alzheimer's disease (AD), Parkinson's disease (PD), and schizophrenia (SCZ) have different pathological mechanisms but share some common neurodegenerative features, such as gradual loss of neuronal structure and function. Dopamine beta-hydroxylase (DBH), a gene located in the chromosomal region 9q34, plays a crucial role in the process of converting dopamine into norepinephrine (NE). Several case-control studies have reported this pathway in the pathogenesis of AD, PD and SCZ. However, the results are controversial. **Methods:** We conducted a meta-analysis to estimate the associations between polymorphisms in this gene and AD, PD and SCZ. Seven databases (PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), Wan Fang, SZ Gene and AD Gene) were searched to identify eligible studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the associations of DBH variants with AD, PD and SCZ susceptibility. **Results:** A total of 41 studies involving 10506 cases and 15083 controls were included in our meta-analysis. The analysis results indicated that a lack of association ($P > 0.05$) was observed between most of the currently available DBH polymorphisms and the neurological diseases AD, PD and SCZ; however, the DBH rs1611131 (allelic model: OR = 0.889, 95% CI: 0.815 - 0.969; dominant model: OR = 0.868, 95% CI: 0.778 - 0.968), rs2283123 (allelic model: OR = 0.285, 95% CI: 0.095 - 0.862; dominant model: OR = 0.290, 95% CI: 0.094 - 0.897) and rs2007153 (allelic model: OR = 2.196, 95% CI: 1.506 - 3.200; dominant model: OR = 2.985, 95% CI: 1.465 - 6.084; recessive model: OR = 2.729, 95% CI: 1.548 - 4.812) variants were

S. Tang and B. Yao contributed equally to this work.

Zunnan Huang
and Shuhuang Lin

Key Laboratory for Medical Molecular Diagnostics of Guangdong Province, Guangdong Medical University,
No. 1 Xincheng Road, Songshan Lake District, Dongguan 523808 (China)
Tel. +86 13925590670; +86 13537173909, E-Mail zn_huang@yahoo.com; shuhuang_lin@yahoo.com

shown to be significantly associated with the risk of AD (the former variant) and SCZ (the latter two variants). **Conclusion:** On the one hand, most DBH polymorphisms from the currently available loci showed no linkage to AD, PD or SCZ, indicating the lower possibility of these loci serving as genetic markers of the risks of diseases with neurodegenerative characteristics. On the other hand, the DBH rs2283123 and rs2007153 polymorphisms could have opposite effects on SCZ development in Caucasians and be more specific in Croatians, while the DBH rs1611131 minor variant might have a protective effect on AD risk in Caucasians; however, these results require further study.

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Introduction

Alzheimer's disease (AD), Parkinson's disease (PD) and schizophrenia (SCZ) all have neurodegenerative characteristics, and although they all show different pathogenies and diseased regions, they each result from the gradual loss of neuronal structure and function or even neuronal death [1]. Illustratively, AD is characterized by the loss of neurons and synapses in the cerebral cortex and certain subcortical regions, including the temporal lobe, regions of the frontal cortex, the cingulate gyrus and the locus coeruleus (LC) in the brainstem [2]; PD is pathologically represented by a degeneration of dopaminergic neurons in the substantia nigra and noradrenergic neurons in the LC [3]; and SCZ is a mental disease that manifests as gradual atrophy of the temporal and parietal lobe as well as enlargement of ventricular regions [4]. Such diseases cause enormous damage to patients' cognitive and behavioral functions [5-7], which seriously reduces their quality of lives. Approximately 29.8, 6.2, and 23.6 million people are estimated to develop AD, PD and SCZ per year, respectively [8, 9]. Although the mechanisms of these three diseases remain unclear, studies have demonstrated that they have common genetic backgrounds and share multiple environmental risk factors. More recently, genome-wide association studies (GWAS) and sequencing approaches have been widely used to discover low-frequency disease risk alleles, and thousands of susceptibility loci might predispose individuals to multiple neurodegenerative diseases [10]. An expected observation for risk variants is shared across diseases. Several genes are associated with AD, PD and SCZ and are included in the shared dopamine (DA) system network, including monoamine oxidase A (MAOA) [11-12], monoamine oxidase B (MAOB) [13-16], catechol-O-methyltransferase (COMT) [17-19] and dopamine beta-hydroxylase (DBH) [20-24]. Identification of these loci could help us better understand the mechanisms underlying the development of and cognitive dysfunction in AD, PD, and SCZ and provide biomarkers for their risk of susceptibility.

The dopamine beta-hydroxylase (DBH) protein is a member of the DA system, which catalyzes the oxidative hydroxylation of DA to norepinephrine (NE) [25]. The enzyme DBH is specifically expressed by noradrenergic neurons, including those in the LC and peripheral nerve terminals [26]. Existing in both soluble and membrane-bound forms, DBH is the only catecholamine synthetase that is expressed in synaptic vesicles [25]. The enzymatic activity of DBH modulates NE levels and further influences executive and motor function as well as reward perception in humans [22], characterized by wide interindividual variation regulated by genetic inheritance [27]. The DBH gene, located in the chromosomal region 9q34 and also known as dopamine beta-monooxygenase (DBM), has an approximately 23 kb sequence that comprises 12 exons.

Because the DBH enzyme plays a key role in the metabolism of DA and NE in the central nervous system (CNS), mutations in its sequence might participate in progressive structural or functional neuronal damage, ultimately resulting in neurodegenerative disease. Thus, it can be logically hypothesized that single nucleotide polymorphisms (SNPs) of DBH could be genetic markers of the risks of AD, PD and SCZ. Many GWAS and case-control studies have investigated the relationship of DBH polymorphisms with these three diseases, and it was even reported that DBH polymorphisms, such as variations in exons of rs1108580, rs5320,

MspI, and rs4531 and introns of 5'-Ins/Del, rs1611115, rs1611131, and rs2519152, could play a role in the pathophysiologies of AD [20-24], PD [28-33] and SCZ [34-49].

Available studies have reported relationships between DBH polymorphisms and the risk of developing AD, PD and SCZ with discrete data, controversial conclusions and insufficient sample sizes. For example, Healy D.G. et al. first reported that the DBH rs1611115 TT genotype genetically determined low serum DBH activity and protected against PD among a United Kingdom (UK) Caucasian population in 2004 [29], whereas two reproductive studies by Chun L.S. et al. in 2007 and Ross O. et al. in 2008 showed no evidence of association between this polymorphism and PD susceptibility [28, 30]; however, a recent genetic association research by Shao P. et al. in 2016 indicated that the TT genotype may lead to a higher risk of PD occurrence than the common genotype CC [31]. Conflicting results have also been published on variations of DBH rs2519152 [31] and other loci [29, 31].

To date, no systematic reviews or meta-analyses of these associations have been conducted to address the issues of inconsistency, insufficiency, and especially nonsystematicness. Thus, we obtained available evidence from all previously published studies concerning the association between DBH SNPs and susceptibility to AD, PD and SCZ and carried out a meta-analysis to estimate this genetic relationship association.

Materials and Methods

Search strategies

Two reviewers systematically searched literature from the PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), Wan Fang, SZ Gene (<http://www.SZgene.org>) and AD Gene (<http://www.ADgene.org>) databases with no language restrictions through January 14th, 2018 using the keywords Alzheimer Disease, Parkinson Disease, Schizophrenia, Dopamine beta-hydroxylase, Polymorphism, etc.. Detailed search strategies are reported in the supplementary materials (For all supplemental material see www.karger.com/d10.1159/000495238). An additional manual search was performed according to references cited in the original literatures or previous reviews.

Literature identification

The suitable studies were selected based on the following inclusion criteria: (I) studies assessing the association of DBH polymorphisms with risks of AD, PD or SCZ; (II) original studies performed using a case-control or cohort design and involving human subjects; (III) studies providing sufficient allelic (e.g., W and M) or genotypic (e.g., WW, WM and MM) data that contained controls with genotypes in Hardy-Weinberg equilibrium (HWE). Studies that did not meet the above inclusion criteria were excluded from our meta-analysis.

Data extraction

For eligible studies, the following data were extracted: (I) the first author's name and publication year; (II) the geographic areas, ethnicities and ages of the participants; (III) the numbers of cases and controls in populations carrying different allelic or genotype statuses; and (IV) the diagnostic criteria for AD, PD or SCZ used in the studies. This step was independently completed by two reviewers. Any disagreement was resolved by discussion with a third reviewer. For studies with overlapping data, that with the largest sample size was included in this meta-analysis.

Methodological quality assessment

Newcastle-Ottawa Scale (NOS) criteria were used to assess the quality of the retrieved studies, which included three aspects: object selection, comparability and exposure assessment [50]. Studies with at least six points were considered high-quality.

Statistical analyses

For each study included in this meta-analysis, the χ^2 test was used to detect whether the observed genotype frequencies among the control groups conformed to Hardy-Weinberg equilibrium (HWE). A χ^2

test *P* value greater than 0.05 suggested that the study sample was representative of the population in the corresponding area.

Odds ratios (ORs) with 95% confidence intervals (CIs) were utilized as effect sizes to evaluate the strengths of the associations between the DBH polymorphisms and risks of AD, PD and SCZ under three genetic models: (I) the allelic model (M vs. W), (II) the dominant model (MM+WM vs. WW), and (III) the recessive model (MM vs. WM+WW). Subgroup analysis was performed to confirm their associations among different ethnicities.

Between-study heterogeneity was assessed by the I^2 statistic from the χ^2 -based Q test [51]. If $I^2 < 50\%$, the fixed-effect model (Mantel-Haenszel method) would be applied to calculate the pooled OR (for pooled estimation) [52]. Otherwise, the random-effects model (DerSimonian-Laird method) was employed to complete this work [53]. Once significant heterogeneity was found, meta-regression [54] would be performed based on the potential confounding factors, including the year, language, ethnicity, diagnose criteria, etc., to determine the source of heterogeneity observed.

For loci with more than three datasets, sensitivity analysis was performed to detect whether the results were considerably influenced by any single study. Simultaneously, Begg's funnel plots constructed by the trim and fill method and quantitative tests were used to estimate publication bias in the included studies.

All analyses were performed using STATA version 14.0 software (STATA Corporation, College Station, TX, USA) with the metan command [55].

Results

Literature search results

Fig. 1 shows a flow chart describing the procedure used to select the eligible studies included in our analysis. The comprehensive search strategy initially identified 429 potential articles (AD: *n* = 55, PD: *n* = 126, SCZ: *n* = 248). Among them, 97 studies were duplicates (AD: *n* = 8, PD: *n* = 20, SCZ: *n* = 69). After removing these duplicates, 332 publications were retained (AD: *n* = 47, PD: *n* = 106, SCZ: *n* = 179), including 153 (AD: *n* = 26, PD: *n* = 73, SCZ: *n* = 54) articles on unrelated genes and 119 (AD: *n* = 14, PD: *n* = 15, SCZ: *n* = 90) articles whose studies did not utilize a case-control or cohort design. Thus, these 272 studies were excluded, and 60 publications remained (AD: *n* = 7, PD: *n* = 18, SCZ: *n* = 35). Among the remaining 60 articles, 31 (AD: *n* = 1, PD: *n* = 11, SCZ: *n* = 19) lacked sufficient allelic or genotypic data. Detailed genotype data were used for the HWE test, and two studies (AD: *n* = 1, PD: *n* = 1, SCZ: *n* = 0) were excluded because they were not in equilibrium. Finally, 27 articles, including 41 eligible studies, were included in this meta-analysis: 7 studies on AD [20-24], 7 studies on PD [28-33] and 27 studies on SCZ [34-49].

Fig. 1. Flow diagram of the process used to select eligible studies.

Main characteristics of the included studies

Table 1 presents the main characteristics of the 41 studies utilized in this meta-analysis. These studies were published from 1996 to 2016. Among them, 25 studies involved Caucasian populations (AD: $n = 5$ [20-22], PD: $n = 3$ [28-30], SCZ: $n = 17$ [34-37, 44-46, 48]), and 16 studies involved Asian populations (AD: $n = 2$ [23, 24], PD: $n = 4$ [31-33], SCZ: $n = 10$ [38-43, 47, 49]). Additionally, two diagnostic criteria were used among the AD studies included (DSM-IV [56] and NINCDS-ADRDA [57]), two criteria were used for PD studies (UK PD Society Brain Bank Clinical Diagnostic Criteria (UK-PDSBB) [58] and Standard for Second National conference on Cone Diseases), and three criteria were used for SCZ studies (DSM-IV [56], DSM-III-R [56] and ICD-10 [59]). Using the methodological quality assessment according to NOS, all the included studies had scores greater than six and were considered high-quality (Table 2). Detailed genotype data from each original study are shown in Table S1.

Association between DBH and AD

In this meta-analysis, a total of seven studies involving 2618 cases and 6849 controls, including five for rs1611115 [20-24], one for rs5320 and one for rs1611131 [20], were collected to investigate the association between DBH polymorphisms and AD development. Combined data revealed that the collection of DBH polymorphisms was not statistically significantly associated with the risk of AD under any of the three genetic models (allelic model: $P = 0.714$, dominant model: $P = 0.837$, and recessive model: $P = 0.607$). The results of these three genetic comparisons also indicated a lack of statistical association between the rs1611115 polymorphism (allelic model: $P = 0.132$, dominant model: $P = 0.146$, and recessive model: $P = 0.425$) and susceptibility to AD (Fig. 2a and Table 3). Subgroup analysis by ethnicity further suggested no association between this polymorphism and AD in either Caucasian or Asian populations (Table 4). In addition, the other two loci presented in only one study each; the DBH rs5320 polymorphism showed no relationship with AD (allelic model: $P = 0.252$, dominant model: $P = 0.298$, and recessive model: $P = 0.394$), while the DBH rs1611131 polymorphism was suggested to be statistically associated with a decreasing risk of AD under the allelic (OR = 0.889, 95% CI: 0.815-0.909, $P = 0.008$) and dominant (OR = 0.868, 95% CI: 0.778-0.968, $P = 0.011$) models but not under the recessive ($P = 0.118$) model. In summary, the above results indicate that while minor variants of rs1611131 might play a protective role in AD development, no associations of the rs1611115 or rs5320 polymorphisms as well as the combination of all three DBH loci with AD risks were observed.

Association between DBH and PD

A meta-analysis of the association between DBH polymorphisms and PD risk included seven [28-33] studies involving a total of 3482 cases and 4086 controls, including four for rs1611115 [28-31], two for rs2519152 [32, 33], and one for rs732833 [31]. The analysis results showed that no associations between a collection of all three DBH polymorphisms with susceptibility to PD was observed in three genetic patterns (allelic model: $P = 0.899$, dominant model: $P = 0.994$, and recessive model: $P = 0.767$, shown in Fig. 2b and Table 3). From the viewpoint of each DBH locus, a lack of association was also found between the polymorphisms of two loci and PD risk in more than one study (rs1611115: allelic model: $P = 0.742$, dominant model: $P = 0.787$, recessive model: $P = 0.971$; rs2519152: allelic model: $P = 0.612$, dominant model: $P = 0.577$, recessive model: $P = 0.655$) (Table 3). In subgroup analysis by ethnicity, no association between the rs1611115 polymorphism and PD development was observed among Caucasians (allelic model: $P = 0.575$, dominant model: $P = 0.631$, recessive model: $P = 0.582$), but the association was statistically significant in Asians, represented by only one study under the allelic and dominant genetic models (allelic model: OR = 1.814, 95% CI: 1.167 – 2.821, $P = 0.008$, dominant model: OR = 1.979, 95% CI: 1.119 – 3.498, $P = 0.019$, recessive model: $P = 0.078$) (Table 4). In addition, the rs732833 polymorphism, which presented in only one study, was also not associated with the risk of PD under any of the three genetic models (allelic model: $P = 0.416$, dominant model: $P = 0.523$, recessive model: $P = 0.416$, shown in Table 3). In summary, the above results suggested that no associations exists between the DBH rs1611115, rs2519152, and rs732833 polymorphisms individually or in combination with the risk of developing PD.

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Table 1. Main characteristics of studies included in the meta-analysis. NA: Not available; HWE: Hardy-Weinberg equilibrium; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; NINCDS-ADDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; UK-PDSBB: UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders-III-R; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders-IV-TR; BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision

Disease	Locus	Author	Year	Country	Race	Case	Control	Case age	Control age	HWE	Diagnostic criteria	Quality	References		
										χ^2	P				
AD	rs1611115	Combarros O. (1)	2010	Mixed	Caucasian	1611	6201	73.0-85.2	71.3-83.0	1.74	0.188	CERAD or NINCDS-ADIRDA	8	20	
		Mateo I.	2005	Spain	Caucasian	266	273	58-98	63-100	0.00	0.984	NINCDS-ADIRDA	6	21	
		Mustapić M.	2013	Croatian	Caucasian	207	90	80-71	78.0-81.1	0.05	0.829	DSM-IV and NINCDS-ADIRDA	8	22	
		Komatsu M.	2014	Japan	Asian	201	130	65.4-91.1	65.2-100.0	0.00	0.959	NINCDS-ADIRDA	6	23	
		Meng Y.	2015	China	Asian	285	124	82-66.9	78.0-88.1	0.32	0.569	DSM-IV and NINCDS-ADIRDA	7	24	
rs5320	Combarros O. (2)	2010	Mixed	Caucasian	1659	6232	73.0-85.2	71.3-83.0	0.00	0.991	CERAD or NINCDS-ADIRDA	8	20		
rs1611131	Combarros O. (3)	2010	Mixed	Caucasian	1647	6193	73.0-85.2	71.3-83.0	0.00	0.979	CERAD or NINCDS-ADIRDA	8	20		
PD	rs1611115	Chun L.S.	2007	NA	Caucasian	1186	1244	67.9 ± 10.6	66.9 ± 14.1	0.61	0.434	Standardized clinical diagnostic criteria for PD	8	28	
		Healy D.	2004	British German Spanish Italian	Caucasian	809	637	NA	NA	3.03	0.082	the modified Queen Square Brain Bank criteria for PD	7	29	
		Ross O.	2008	Polish US Irish Norwegian	Caucasian	1037	1659	NA	NA	0.57	0.448	Published criteria	7	30	
		Shao P. (1)	2016	Southern China	Asian	95	100	61.32±6.51	63.84±7.63	0.07	0.791	UK-PDSBB	8	31	
		Song Q.X.	2015	Chinese	Asian	221	229	67.96±9.79 65.22±12.09	76.07±10.38 66.37±10.78	2.50	0.114	UK-PDSBB	8	32	
SCZ	rs732833 5'-Ins/Del	Xu L.	2002	Chinese	Asian	134	217	64.4±10.3	NA	0.11	0.740	Standard for Second National conference on Core Diseases	9	33	
		Shao P. (2)	2016	Southern China	Asian	95	100	61.32±6.51	63.84±7.63	2.95	0.086	UK-PDSBB	8	31	
		Barlas I. (1)	2012	Turkey	Caucasian	87	139	30.5 ± 10.6	NA	0.07	0.791	DSM-IV	7	34	
		Meszaros K.	1996	Austria	Caucasian	64	60	NA	NA	1.07	0.302	DSM-III-R	7	35	
		Shakiba M.	2016	Iran	Caucasian	109	116	NA	NA	0.04	0.847	DSM-IV-TR	6	36	
		Yamamoto K. (1)	2003	French, Canadians	Caucasian	106	120	NA	NA	0.26	0.609	BPRS or CGI	6	37	
		Li H.	2016	China	Asian	733	544	48.0 ± 9.5	45.7 ± 12.6	3.50	0.061	DSM-IV	8	38	
		Park J. (1)	2007	Korean	Asian	140	161	NA	NA	0.51	0.477	DSM-IV	7	39	
		Zhang X.Y.	2012	China	Asian	636	396	47.3±9.8	NA	0.10	0.757	DSM-IV	8	40	
		Zhou N.	2013	China	Asian	747	625	24.6 ± 9.9	NA	0.32	0.573	DSM-IV	7	41	
		Barlas I. (2)	2012	Turkey	Caucasian	87	139	19.9-41.1	NA	0.13	0.717	DSM-IV	8	34	
		Yamamoto K. (2)	2003	French, Canadians	Caucasian	106	120	NA	NA	0.87	0.351	BPRS or CGI	6	37	
		Park J. (2)	2007	Korean	Asian	140	161	NA	NA	2.56	0.109	DSM-IV	7	39	
		Shi J.J.	2003	China	Asian	217	109	30.4±11.4	31.2±6.5	2.68	0.102	DSM-IV	7	42	
		Srivastava V.	2010	India	Asian	215	215	29.34 ± 8.92	34.63 ± 12.47	1.44	0.230	DSM-IV	7	43	
rs1611115		Jonsson E.	2003	Finland	Caucasian	155	436	42.7 ± 13.4	41.0 ± 16.9	0.08	0.775	DSM-III-R	7	44	
		Park J. (3)	2007	Korean	Asian	140	161	NA	NA	3.31	0.069	DSM-III-R	7	39	
		Pal P. (1)	2009	Croatia	Caucasian	103	131	43.6 ± 10.6	50.3 ± 7.5	0.00	0.969	ICD-10	7	45	
		Williams H.	1999	NA	Caucasian	178	178	41 ± 13.1	40 ± 11.9	0.86	0.353	DSM-III-R	7	46	
		Iwata Y.	2003	Japan	Asian	51	148	87-15.9	14-28	0.01	0.934	DSM-IV	7	47	
		Wei J.	1996	Britain	Caucasian	174	72	24.8-45.8	26.1-53.3	0.28	0.596	NA	6	48	
		Long J.X.	2016	China	Asian	691	698	32.81 ± 11.70	32.78 ± 12.06	1.53	0.216	ICD-10	8	49	
		Pal P. (2)	2009	Croatia	Caucasian	103	131	43.6 ± 10.6	50.3 ± 7.5	0.01	0.910	ICD-10	7	45	
		Pal P. (3)	2009	Croatia	Caucasian	103	131	43.6 ± 10.6	50.3 ± 7.5	0.00	0.949	ICD-10	7	45	
		Pal P. (4)	2009	Croatia	Caucasian	103	131	43.6 ± 10.6	50.3 ± 7.5	0.00	0.955	ICD-10	7	45	
		rs3025399	Pal P. (5)	2009	Croatia	Caucasian	103	131	43.6 ± 10.6	50.3 ± 7.5	0.06	0.808	ICD-10	7	45
		rs1076150	Pal P. (6)	2009	Croatia	Caucasian	103	131	43.6 ± 10.6	50.3 ± 7.5	0.00	0.987	ICD-10	7	45
		rs2283123	Pal P. (7)	2009	Croatia	Caucasian	103	131	43.6 ± 10.6	50.3 ± 7.5	0.42	0.518	ICD-10	7	45
		rs2007153	Pal P. (8)	2009	Croatia	Caucasian	103	131	43.6 ± 10.6	50.3 ± 7.5	0.00	0.964	ICD-10	7	45

the development of SCZ under three genetic models (allelic model: $P = 0.342$, dominant model: $P = 0.563$, and recessive model: $P = 0.312$) (Fig. 2c and Table 3). For four loci presenting in multiple studies, statistical results showed that their polymorphisms were not linked to the risk of developing SCZ (5'-Ins/Del: allelic model: $P = 0.563$, dominant model: $P = 0.445$, recessive model: $P = 0.906$; rs1108580: allelic model: $P = 0.750$, dominant model: $P = 0.967$, recessive model: $P = 0.552$; rs1611115: allelic model: $P = 0.684$, dominant model: $P = 0.830$, recessive model: $P = 0.511$; and rs4531: allelic model: $P = 0.279$, dominant model: $P = 0.443$, recessive model: $P = 0.268$) (Table 3). Subgroup analysis by ethnicity further suggested no association between polymorphisms of these loci and SCZ risk in Caucasians or Asians (Table 4). In addition, among nine loci presenting in only one study each, the polymorphisms of seven loci, including MspI, rs1611114, rs1541333, rs77905, rs732833, rs3025399 and rs1076150, showed no association with the risk of SCZ under any of the three genetic comparisons (Table 3). On the other hand, the analysis results indicated that the rs2283123 polymorphism could significantly reduce susceptibility to SCZ in the allelic (OR = 0.285, 95% CI: 0.095-0.862, $P = 0.026$) and dominant (OR = 0.290, 95% CI: 0.094-0.897, $P = 0.032$) models but not in the recessive ($P = 0.597$) model, and the DBH rs2007153 polymorphism significantly increased the risk of developing SCZ under all three models (allelic model: OR = 2.196, 95% CI = 1.506-3.200, $P = 0.000$; dominant model: OR = 2.985, 95% CI = 1.465-6.084, $P = 0.003$; recessive model: OR = 2.729, 95% CI: 1.548-4.812, $P = 0.001$). In summary, the DBH rs2283123 and rs2007153 polymorphisms might influence SCZ risk, but the DBH 5'-Ins/Del, rs1108580, rs1611115, and rs4531 polymorphisms and the combination of all 13 DBH loci were not associated with the risk of SCZ development.

Association of DBH with diseases with neurodegenerative features, including AD, PD, and SCZ

In this systematic analysis, a total of 41 studies involving 10506 cases and 15083 controls, including seven on AD [20-24], seven on PD [28-33], and twenty-seven on SCZ [34-49], were used in combination to investigate the association between a combination of all the available DBH polymorphisms and the development of diseases with neurodegenerative features, including AD, PD and SCZ. The combined results showed a lack of association between them under three genetic models (allelic model: $P = 0.330$, dominant model: $P = 0.755$, and recessive model: $P = 0.509$, shown in Fig. 2d and Table 3). In subgroup analysis by ethnicity, no associations of the sixteen DBH polymorphisms with the risks of these three diseases were found among either Caucasians (allelic model: $P = 0.640$, dominant model: $P = 0.741$, and recessive model: $P = 0.875$) or Asians (allelic model: $P = 0.426$, dominant model: $P = 0.524$, and recessive model: $P = 0.515$) (Table 4). In summary, the previously reported DBH polymorphisms did not have any cumulative effect on the susceptibility to diseases with neurodegenerative features, including AD, PD and SCZ.

Table 2. Quality assessment scheme for the included literatures (Newcastle-Ottawa Scale)

Disease	Author	Year	Selection				Comparability	Exposure			Total
			I	II	III	IV		VI	VII	VIII	
AD	Combarros O.	2010	*	*	*		**	*	*	*	8
	Mateo I.	2005	*		*		*	*	*	*	6
	Mustapic M.	2013	*	*	*		**	*	*	*	8
	Komatsu M.	2014	*		*		*	*	*	*	6
	Meng Y.	2015	*	*	*		*	*	*	*	7
PD	Chun L.S.	2007	*	*	*		**	*	*	*	8
	Healy D.	2004	*	*			**	*	*	*	7
	Ross O.	2008	*		*		**	*	*	*	7
	Shao P.	2016	*	*	*		**	*	*	*	8
	Song Q.X.	2015	*	*	*		**	*	*	*	8
	Xu L.	2002	*	*	*	*	**	*	*	*	9
SCZ	Barlas I.	2012	*		*		**	*	*	*	7
	Meszaros K.	1996	*		*		**	*	*	*	7
	Shakiba M.	2016	*	*	*		*	*	*	*	6
	Yamamoto K.	2003	*		*		*	*	*	*	6
	Li H.	2016	*	*	*	*	*	*	*	*	8
	Park J.	2007	*	*	*		*	*	*	*	7
	Zhang X.Y.	2012	*	*	*		**	*	*	*	8
	Zhou N.	2013	*		*		**	*	*	*	7
	Shi J.J.	2003	*	*	*		**	*	*	*	8
	Srivastava V.	2010	*		*		**	*	*	*	7
	Jonsson E.	2003	*		*		**	*	*	*	7
	Pal P.	2009	*	*	*		*	*	*	*	7
	Williams H.	1999	*		*		**	*	*	*	7
	Iwata Y.	2003	*		*		**	*	*	*	7
	Wei J.	1996	*		*		*	*	*	*	6
	Long J.X.	2016	*	*	*		**	*	*	*	8

Heterogeneity analysis

In the abovementioned meta-analysis, high heterogeneity was found in analyses of the associations of the collection of DBH polymorphisms with PD risk (allelic model: $I^2 = 75.0\%$; dominant model: $I^2 = 69.5\%$; recessive model: $I^2 = 56.7\%$) (shown in Table 3). In addition, significant heterogeneity was also observed in the investigation of correlations between both DBH rs1611115 (allelic model: $I^2 = 80.8\%$, dominant model: $I^2 = 71.2\%$ and recessive model: $I^2 = 76.4\%$) and rs2519152 (allelic model: $I^2 = 86.6\%$ and dominant model: $I^2 = 87.7\%$) and PD risk. Meta-regression analysis was performed to explore whether the source of the abovementioned between-study heterogeneity was due to the publication year, ethnicity, diagnostic criteria, NOS score or sample size. Statistical results from the meta-regression are

Fig. 2. Forest plots of the association between combined DBH polymorphisms and the risks of Alzheimer's disease (a), Parkinson's disease (b), schizophrenia (c) and all the three diseases (d) in the allelic model.

displayed in Table S2. However, no factors could eliminate or reduce the heterogeneity to an acceptable level (all *P*-regression > 0.05).

Sensitivity analysis and publication bias

Sensitivity analysis showed that the pooled ORs were not significantly altered for the DBH rs1611115, 5'-Ins/Del, and rs1108580 polymorphisms presenting in more than three studies on AD, PD and SCZ when all the included studies were excluded one by one, which indicated that our results were robust and reliable (data not shown). According to the shapes

Table 3. Meta-analysis of DBH polymorphisms in Alzheimer's disease, Parkinson's disease, and schizophrenia. Note: *Cannot be calculated; F: Fixed-effect model (the Mantel-Haenszel method); R: Random-effects model (the DerSimonian-Laird method); *P_H*: *P* value of homogeneity; OR: Odds ratio; CI: Confidence interval; NA: Not available

Disease	Locus	N	Effect model	Allelic model				Dominant model				Recessive model											
				Test of homogeneity	Test of association	Effect model	Test of homogeneity	Test of association	Effect model	Test of homogeneity	Test of association	Effect model	Test of homogeneity	Test of association	Effect model								
			χ^2	P_h	P	OR	95%CI	χ^2	P_h	I^2	OR	95%CI	P	χ^2	P_h	F	OR	95%CI	P				
AD	Total	7	R	11.11	0.085	46.0%	0.990	0.935-1.047	0.714	R	10.08	0.121	40.5%	0.993	0.928-1.063	0.837	F	4.24	0.644	0.0%	0.962	0.828-1.116	
	rs1611115	C/T	5	F	0.510	0.973	0.0%	1.066	0.981-1.158	0.132	F	0.41	0.981	0.0%	1.077	0.975-1.190	0.146	F	0.66	0.956	0.0%	1.095	0.876-1.425
	rs5320	Ala/Thr	1	F	NA	NA	NA	1.101	0.934-1.297	0.252	F	NA	NA	NA	1.096	0.922-1.301	0.298	F	NA	NA	NA	1.463	0.610-3.508
	rs1611131	A/G	1	F	NA	NA	NA	0.889	0.815-0.969	0.008	F	NA	NA	NA	0.868	0.778-0.968	0.011	F	NA	NA	NA	0.848	0.689-1.043
	Total	7	R	24.01	0.001	75.0%	1.012	0.844-1.213	0.899	R	19.65	0.003	69.5%	0.999	0.818-1.221	0.994	R	13.85	0.031	56.7%	1.056	0.735-1.518	
PPD	rs1611115	C/T	4	R	15.59	0.001	80.8%	1.036	0.838-1.281	0.742	R	10.40	0.015	71.2%	1.029	0.836-1.267	0.787	R	12.69	0.005	76.4%	1.010	0.598-1.703
	rs2519152	G/A	2	R	7.47	0.006	86.6%	0.823	0.387-1.750	0.612	R	8.15	0.004	87.7%	0.770	0.308-1.926	0.577	F	0.27	0.602	0.0%	1.150	0.622-2.216
	rs732833	A/G	1	F	NA	NA	NA	1.185	0.787-1.785	0.416	F	NA	NA	NA	1.212	0.672-2.189	0.523	F	NA	NA	NA	1.462	0.586-3.646
	Total	27	F	38.92	0.050	33.2%	1.028	0.971-1.089	0.342	F	36.47	0.083	28.7%	1.024	0.944-1.112	0.563	F	25.94	0.411	3.6%	1.056	0.950-1.175	
	5'-Ins/Del	Ins/Del	8	F	5.23	0.632	0.0%	1.024	0.944-1.112	0.563	F	8.00	0.333	12.5%	1.049	0.928-1.185	0.445	F	1.23	0.990	0.0%	1.009	0.872-1.167
SCZ	rs1108580	A/G	5	F	0.96	0.916	0.0%	0.974	0.825-1.148	0.750	F	4.37	0.359	8.4%	0.995	0.798-1.242	0.967	F	4.90	0.298	18.3%	0.901	0.640-1.269
	rs1611115	C/T	3	F	3.28	0.194	39.1%	1.045	0.845-1.292	0.684	F	3.81	0.149	47.6%	1.028	0.797-1.326	0.830	F	1.87	0.393	0.0%	1.224	0.670-2.239
	rs4531	G/T	2	F	0.00	0.946	0.0%	1.322	0.797-2.194	0.279	F	0.01	0.903	0.0%	1.242	0.714-2.161	0.443	F	NA*	NA*	NA*	2.543	0.487-13.286
	MspI	A1/A2	1	F	NA	NA	NA	1.222	0.812-1.839	0.226	F	NA	NA	NA	1.117	0.643-1.940	0.695	F	NA	NA	NA	1.638	0.740-3.627
	rs1611114	C/T	1	F	NA	NA	NA	0.951	0.819-1.106	0.115	F	NA	NA	NA	0.889	0.713-1.110	0.299	F	NA	NA	NA	1.013	0.779-1.316
	rs1541333	C/G	1	F	NA	NA	NA	1.165	0.807-1.680	0.415	F	NA	NA	NA	1.220	0.690-2.158	0.494	F	NA	NA	NA	1.227	0.655-2.296
	rs77905	C/T	1	F	NA	NA	NA	0.995	0.690-1.433	0.796	F	NA	NA	NA	1.015	0.569-1.812	0.960	F	NA	NA	NA	0.968	0.522-1.795
	rs732833	A/G	1	F	NA	NA	NA	0.703	0.482-1.027	0.068	F	NA	NA	NA	0.634	0.373-1.076	0.091	F	NA	NA	NA	0.631	0.298-1.337
	rs3025399	A/C	1	F	NA	NA	NA	1.020	0.576-1.805	0.946	F	NA	NA	NA	1.058	0.567-1.974	0.860	F	NA	NA	NA	0.632	0.457-1.632
	rs1076150	G/A	1	F	NA	NA	NA	1.269	0.874-1.842	0.211	F	NA	NA	NA	1.336	0.779-2.291	0.293	F	NA	NA	NA	1.420	0.702-2.870
	rs2283123	C/T	1	F	NA	NA	NA	0.285	0.095-0.862	0.026	F	NA	NA	NA	0.290	0.094-0.897	0.032	F	NA	NA	NA	0.420	0.101-10.425
rs2007153	A/G	1	F	NA	NA	NA	2.196	1.506-3.200	0.000	F	NA	NA	NA	2.985	1.465-6.084	0.003	F	NA	NA	NA	2.729	1.548-4.812	
All	Total	41	R	41.84	0.001	57.0%	1.039	0.962-1.122	0.330	F	30.97	0.029	41.9%	1.008	0.959-1.060	0.755	F	23.00	0.191	21.7%	1.029	0.946-1.120	

Table 4. Subgroup analysis of DBH polymorphisms on Alzheimer's disease, Parkinson's disease, schizophrenia by ethnicity. Note: F: Fixed-effect model (the Mantel-Haenszel method); R: Random-effects model (the DerSimonian-Laird method); P_h : P value of homogeneity; OR: Odds ratio; CI: Confidence interval; NA: Not available

Disease	Locus	N	Population	Effect model	Allelic model						Effect model	Dominant model						Effect model	Recessive model								
					Test of homogeneity			OR	95%CI			P	Test of homogeneity			OR	95%CI		P	Test of homogeneity			OR	95%CI		P	
					χ^2	P_h	I^2		χ^2	P_h			I^2	χ^2	P_h		I^2			χ^2	P_h	I^2		χ^2	P_h		I^2
AD	rs1611115	C/T	3	Caucasian	F	0.38	0.825	0.0%	1.068	0.979-1.165	0.141	F	0.27	0.874	0.0%	1.082	0.975-1.202	0.139	F	0.30	0.862	0.0%	1.079	0.854-1.364	0.523		
			2	Asian	F	0.11	0.741	0.0%	1.050	0.799-1.381	0.725	F	0.05	0.824	0.0%	1.025	0.739-1.422	0.882	F	0.21	0.644	0.0%	1.267	0.593-2.706	0.541		
PD	rs1611115	C/T	3	Caucasian	R	8.14	0.017	75.4%	0.951	0.797-1.134	0.575	R	4.62	0.099	56.7%	0.962	0.822-1.126	0.631	R	9.21	0.01	78.3%	0.863	0.509-1.461	0.582		
			1	Asian	F	NA	NA	NA	1.814	1.167-2.821	0.008	F	NA	NA	NA	1.979	1.119-3.498	0.019	F	NA	NA	NA	2.484	0.903-6.831	0.078		
SCZ	5'-Ins/Del Ins/Del	4	Caucasian	F	0.30	0.961	0.0%	0.931	0.764-1.134	0.478	F	0.12	0.989	0.0%	0.878	0.638-1.207	0.422	F	0.74	0.864	0.0%	0.946	0.687-1.302	0.732			
			4	Asian	F	3.84	0.279	22.0%	1.045	0.955-1.144	0.337	R	6.46	0.091	53.6%	1.049	0.854-1.288	0.649	F	0.30	0.961	0.0%	1.026	0.871-1.208	0.758		
	rs1108580	A/G	2	Caucasian	F	0.06	0.812	0.0%	2.045	0.723-1.232	0.671	F	0.07	0.786	0.0%	0.820	0.540-1.245	0.353	F	0.28	0.594	0.0%	1.069	0.678-1.686	0.774		
			3	Asian	F	0.82	0.665	0.0%	3.045	0.804-1.225	0.944	F	3.16	0.206	36.6%	1.073	0.827-1.394	0.595	F	3.15	0.207	36.4%	0.722	0.430-1.214	0.220		
	rs1611115	C/T	2	Caucasian	R	2.95	0.086	66.1%	4.045	0.663-1.627	0.869	R	2.76	0.097	63.7%	1.061	0.625-1.801	0.827	F	0.84	0.359	0.0%	1.035	0.522-2.054	0.921		
			1	Asian	F	NA	NA	NA	5.045	0.635-1.415	0.794	F	NA	NA	NA	0.838	0.524-1.340	0.460	F	NA	NA	NA	2.358	0.579-9.610	0.231		
	rs4531	G/T	1	Caucasian	F	NA	NA	NA	6.045	0.786-2.211	0.296	F	NA	NA	NA	1.233	0.698-2.177	0.470	F	NA	NA	NA	2.543	0.487-13.286	0.268		
			1	Asian	F	NA	NA	NA	7.045	0.129-16.002	0.769	F	NA	NA	NA	1.440	0.128-16.225	0.768	NA	NA	NA	NA	NA	NA	NA		
All	Total	25	Caucasian	R	53.28	0.001	55.0%	8.045	0.942-1.103	0.640	F	38.68	0.030	37.9%	0.991	0.940-1.045	0.741	F	33.52	0.094	28.4%	1.008	0.909-1.118	0.875			
		16	Asian	F	21.14	0.132	29.0%	9.045	0.962-1.096	0.426	F	27.40	0.026	45.3%	1.030	0.941-1.127	0.524	F	11.27	0.665	0.0%	1.043	0.919-1.183	0.515			

of Begg's funnel plots created by the trim and fill method, no asymmetric signal was observed under the allelic model (Fig. 3 shows the funnel plot for the allelic model to analyze the publication bias of the association of the DBH 5'-Ins/Del polymorphism with SCZ risk). Further quantitative tests also suggested no publication bias for these SNPs and the risks of AD, PD and SCZ (Table 5).

Discussion

As a member of the DA system, the DBH enzyme catalyzes the oxidative hydroxylation of DA to NE in the CNS. A recent study reported the DBH crystal structure, revealing four domains (the DOMON (dopamine b-monooxygenase N-terminal) domain, which forms a possible metal-binding site and a ligand-binding pocket; the catalytic CuH and CuM domains; and the C-terminal dimerization domain), providing new molecular insights into the catalytic mechanism, as well as the destructive disorders of both physiological and neurological origin of the DBH enzyme and the DA system [60]. On the other hand, the enzymatic activity and plasma level of DBH show wide interindividual variation modulated by genetic inheritance [27]. For instance, Mustapic M. et al. (2013) showed significant

Fig. 3. Funnel plot for the allelic model to analyze the publication bias of the association between the DBH 5'-Ins/Del polymorphism and SCZ risk by the trim and fill method.**Table 5.** Reported results of Begg's test to assess risk of publication bias on DBH polymorphisms and Alzheimer's disease, Parkinson's disease, and schizophrenia. Note: P_{Begg} : P value of the Begg's test

Disease	Loci	Test for Publication bias	
		N	P_{Begg}
AD	rs1611115	5	0.806
PD	rs1611115	4	1.000
SCZ	5'-Ins/Del	8	0.266
	rs1108580	5	0.221

effects of DBH rs1611115 and rs6271 on decreased pDBH activity among AD patients [22]; the effect of rs1611115 on pDBH activity in SCZ was also confirmed by Sun Z.L. et al. (2017) [61]. Moreover, numerous studies have demonstrated that variants of the DBH gene have a significant influence on the cognitive phenotypes of neurological diseases. For example, Shao P. et al. (2016) suggested that abnormal cognitive states of PD patients are linked to the DBH rs1611115 variant among the Chinese Han population [31], and the rs1611115 and rs1108580 polymorphisms are significantly correlated with the degree of cognitive impairment in SCZ patients [61]. This evidence suggests that DBH SNPs could be a possible mechanism underlying the progression of AD, PD and SCZ. However, according to our results, DBH polymorphisms might not correlate with the developmental risk of these three diseases.

AD is a classical polygenic disease, but its pathogenic mechanism is still unclear. Many genes, such as apolipoprotein E (APOE) [62], triggering receptor expressed on myeloid cells 2 (TREM2) [63], and methylene tetrahydrofolate reductase (MTHFR) [64], in combination with environmental factors result in a network of interplay in AD development. DBH catalyzes the oxidative hydroxylation of DA to NE, and recent evidence indicated that NE is not only a risk factor but also an actual etiological factor of AD [22]. We collected seven studies on the association of DBH polymorphisms at three loci (rs1611115, rs5320, and rs1611131) with the risk of AD. The analysis results indicated that polymorphisms of these three loci were not associated with AD risk. Although the rs5320 polymorphism might not influence the disease susceptibility and needs to be further evaluated due to a low number of studies being included in the analysis, the conclusion that the rs1611115 polymorphism had no effect on the risk of AD in this retrospective analysis should be quite robust because all five case-control studies included produced negative results (Combarros O. et al. (2010) [20], Mateo I. et al. (2006) [21], Mustapic M. et al. (2013) [22], Komatsu M. et al. (2014) [23], and Meng Y. et al. (2015) [24]). It should be noted that the negative result reported in the study by Combarros O. et al. included in this meta-analysis is discrepant with the positive result in the original publication due to an OR being adjusted by the synergistic factors that the authors utilized (sample source, age, sex and APOE ϵ 4 genotype) [20], but we estimated this association using rough allelic or genotypic data. On the other hand, Combarros O. et al. also found that the correlation between the rs1611115 allele and AD risk were nearly restricted to men [20]. In addition, the interaction between the presence of DBH rs1611115 and the TT genotype of IL1A rs1800587 was also found in the original publication, contributing to the determination of susceptibility to AD [20]. These results suggested that the role of the DBH rs1611115 variant might be influenced by other synergistic factors, such as age, gender and gene-gene interactions, in AD development. The rs1611131 polymorphism was statistically associated with a decreased risk of AD development in the allelic and dominant models but not in the recessive model. The data for this locus also originated from the study by Combarros O. et al., and our result was inconsistent with their negative result, possibly due to the similar confounding adjustment based on a small sample size. Furthermore, our study further illustrated that a combination of polymorphisms of the DBH three loci was not associated with AD risk, indicating that the previously identified DBH SNPs had no cumulative effect on the susceptibility to AD. However, the currently available evidence cannot prove that DBH polymorphisms are independent, risk-free factors underlying the development of AD.

PD is another neurodegenerative disorder commonly studied. Rare variants in monogenic forms have been shown to be connected with the disease at the gene level [65]. Neuropathological analysis of PD indicates that the retrogression of dopaminergic neurons in the substantia nigra leads to a DA deficiency in the corpus striatum [3]. The DBH enzyme is an important member of the DA system, and evidence has shown that under certain conditions, DBH can influence the NE levels in the brain [22]. In addition, previous studies found altered DBH activity in cerebrospinal fluid (CSF) [22], also suggesting that DBH might participate in the pathological mechanism of PD. However, little is known about how the DBH gene modulates DBH enzymatic activity as well as NE levels and further determines the retrogression of dopaminergic neurons in the development and progression of PD. Over

the past few decades, studies have investigated the correlation of DBH polymorphisms with PD risk, but they have displayed controversial results. Available data on the association between three SNPs (rs1611115, rs2519152, and rs732833) and PD risk were collected in our retrospective study. For rs1611115, combined results from all four of the studies included indicated that this SNP is not statistically associated with an increased PD risk, consistent with the results from two individual studies authored by Chun L.S. et al. (2007) [28] and Ross O. et al. (2008) [30] but not with those of the other two studies (Fig. 2B). In the other two original publications, Healy D. et al. (2004) reported that individuals carrying the homozygous DBH rs1611115 TT genotype have protection against PD [29]; conversely, Shao P. et al. (2016) recently found that this variant is likely associated with an increased susceptibility to PD [31]. Different genetic backgrounds from different races may possibly underlie this discrepancy because the former studies involved Caucasians, while the latter studies focused on the Asian population. A comparatively insufficient sample size may also be a probable cause underlying the discrepant results, as it may poorly represent the overall population. For another gene locus, rs2519152, statistical results based on two available studies also demonstrated no correlation between its polymorphism and the risk of developing PD (Fig. 2B and Table 3). This result is in accordance with the conclusion of the newest article by Song Q.X. et al. (2015) [32] but contradicts that of an earlier study by Xu L. et al. (2002) [33], which suggested a protective role of DBH rs2519152 minor variants against the development of PD [33] (Fig. 2B). Both studies were restricted to the Chinese Han population. Thus, further evaluating the link between this polymorphism and PD is necessary to achieve a definitive conclusion. For the third locus (rs732833) in this group, its polymorphism from one study was not associated with PD development (Table 3). In addition, our meta-analysis further illustrated a lack of association between a combination of the polymorphisms of these three loci and the risk of PD, also denoting that DBH SNPs might not have a comprehensive effect on the susceptibility to PD.

SCZ is one of the most severe chronic mental illnesses that presents with characteristic retrogression in the central nervous system (CNS) [66], and the neurodegenerative basis of SCZ remains a matter of debate. Previous studies have reported abnormal neuronal migration and clinical features of aberrant neurodevelopment in the form of soft neurological signs, which might suggest a neurodevelopmental mechanism for SCZ [67]. However, current evidence suggests that SCZ is a complex disorder with neuronal degeneration characteristics. On the basis of autopsy, gliosis was found in the brain tissues of SCZ patients [68], and more recently, Muraleedharan A. et al. (2015) reported substantial DNA damage in SCZ patients based on the detection of proteotoxic stress in cerebral cells [69], which both represent cardinal features of neurodegeneration hinting at neuron depletion. Compared to the classical neurodegenerative diseases AD and PD, the pathophysiological heterogeneity of SCZ might lead to diverse time course and treatment strategies. To date, we still have little knowledge about the neuropathology of SCZ [7], but the DA hypothesis is a leading theory underlying its etiology [70]. In 2014, Oliver H. et al. reported a presynaptic hyperdopaminergic abnormality in SCZ patients [71]. Cubells J.F. et al. (1998) [72] further implied that DBH activity and the CSF DBH protein level could be regarded as biomarkers of SCZ. Our retrospective study contained data available on the association between polymorphisms of thirteen loci and SCZ risk. Eight, five, three and two independent studies were collected in this meta-analysis containing polymorphisms of 5'-Ins/Del, rs1108580, rs1611115, and rs4531 on the development of SCZ, respectively. The conclusions of these studies on the genetic polymorphisms of these four loci shared considerable similarities. The combined result indicated that variants of these four loci were not statistically associated with SCZ susceptibility. Good consistency and no detectable heterogeneity among all the included studies indicate that our finding are robust (Fig. 2C and Table 3). Simultaneously, statistical analyses of the other seven SNPs (MspI, rs1541333, rs77905, rs732833, rs3025399, rs1076150 and rs1611114), each represented by only one study, demonstrated that they might not influence the susceptibility to SCZ, but these results need to be further confirmed (Fig. 2C and Table 3). On the other hand, Pal P. et al. (2009) found that the rs2007153 polymorphism showed significant allelic

and dominant associations with increased SCZ risk, which was consistent with our results. However, a correlation between rs2283123 and SCZ susceptibility was found under only the allelic model [45], while this association existed under all three genetic models in our meta-analysis. Only two DBH loci were found to be associated with SCZ risk, but the studies in which these loci were reported utilized relatively small sample sizes, and no other published studies have confirmed the association of these two loci with SCZ risk. This discrepancy might be explained by the “winner curse” phenomenon that usually occurs when using the candidate gene approach in which SNP loci are initially detected as associated factors but cannot be frequently identified by subsequent studies [73]. Future studies should focus on these two candidate target SNPs. Additionally, we further illustrated no statistically significant association between SCZ and the cumulative effect of available DBH SNPs.

Neurodegenerative diseases represent disorders resulting from the gradual loss of neuronal function or structure (or from neuronal death) [74]. In addition to classical neurodegenerative diseases, such as AD, PD, Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and Batten's disease (BD), some mental sicknesses, such as SCZ and depression, are newly reported to show the characteristics of neuronal degeneration [69, 75]. Despite the common feature of gradual brain degeneration in patients with these diseases, a common underlying mechanism remains unclarified. In diseases such as AD, PD and SCZ, overphosphorylation of the tau protein is widely observed, leading to the abnormal accumulation and entanglement of nerve fibers, which further causes cerebral cell dysfunction, indicating that these diseases may share some pathogenic characteristics [76-78]. On the other hand, based on the DA dysfunction and low DBH activity found in patients suffering from these diseases [27, 79, 80], genes of the DA system are considered vital candidate genetic targets for all neurodegenerative diseases. DBH, a critical member of the DA system, has been studied in association with the risks of neurodegenerative disease for a long time. We herein provide a comprehensive evaluation of the correlations of common genetic variants in candidate DBH gene loci with three diseases having neurodegenerative features, AD, PD and SCZ. In our findings, except for a few loci (rs1611131, rs2007153 and rs2283123) that might show correlation with neurodegenerative disorders, almost all the available SNPs were not associated with neurodegenerative diseases (Fig. 2D). In particular, DBH rs1611115, one of the most widely investigated DBH loci that was shown to regulate the activity and level of the DBH enzyme in numerous previous studies [22, 27, 81], displayed no association with any of the three diseases in our meta-analysis. Additionally, while the similar neural degeneration characteristics displayed by these three diseases, the fact that the cumulative statistical data displayed a lack of association between DBH loci and the risk of diseases suggest that DBH polymorphisms might not be risk factors underlying the development of disorders with neurodegenerative features. This statistical finding somewhat corresponds to the randomness in the distribution of negative associations between genetic polymorphisms and disease risk because if the results at each locus show a lack of association, their combination should indeed show nonsignificant correlation with the disease. These results could indicate that DBH polymorphisms may not be independent risk factors and thus may not be genetic markers for the risk of AD, PD and SCZ; however, they could still participate in the development of diseases with neurodegenerative characteristics by interacting with other genes.

Meta-analysis is a quantitative statistical analysis tool that can integrate the outcomes of independent studies and provide a more reliable conclusion. To our knowledge, no systematic study has comprehensively estimated the probable relationship between DBH SNPs and neurodegenerative disease. In our research, a thorough and meticulous search was performed to identify all available DBH polymorphisms, providing a comprehensive review of the association between DBH mutation and the risk of diseases with neurodegenerative characteristics, including AD, PD and SCZ. Both the independent role of a single DBH locus and its cumulative effect on these three types of neurological illness were analyzed in our meta-analysis, providing us with a better understanding of the gene-disease association from multiple viewpoints. However, some limitations of this study should also be recognized.

First, the sample sizes of some of the included loci were small. It is worth noting that three significantly associated loci were presented in only one dataset, which might have led to a spurious correlation. Second, heterogeneity was detected in the association studies of some polymorphisms with PD, but we were unable to find the sources of heterogeneity in these polymorphisms according to the available concomitant factors. Third, previous studies suggested that the relationships of SNPs with AD, PD and SCZ might be affected by gender, onset age and carrying statuses of other genes. We could not conduct corresponding subgroup and stratification analyses [82] to further explore in-depth reasons for their association because of insufficient data. Therefore, the conclusions from the studies reviewed in this analysis should be interpreted with caution.

Conclusion

In conclusion, our comprehensive systemic review (a) suggested that most DBH polymorphisms of the currently available loci may not be risk factors for the neurological diseases AD, PD and SCZ and specifically (b) revealed a lack of association between the DBH rs1611115 polymorphism and the development of AD and between the 5'-Ins/Del, rs1108580, rs1611115 and rs4531 variants and the risk of developing SCZ; these results were supported by relatively large sample sizes and are thus robust conclusions. Our comprehensive systemic review also (c) showed that while the rs1611131 and rs2283123 polymorphisms could play a protective role in the risk of AD and SCZ, respectively, rs2007153 variants might be a risk factor for SCZ; however, these three loci were all reported by only one study each. While reliable conclusions might not be drawn for the associations of some DBH polymorphisms with PD due to either high heterogeneity between studies or having only a few case-control studies available for analysis, future well-designed studies with large sample sizes as well as gene-gene and gene-environment interactions are needed to confirm these conclusions.

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Disclosure Statement

The authors declare no conflicts of interest.

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