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Meta analysis of the association of rs7702187 SNP in SEMA5A gene with risk of Parkinson's disease

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Abstract. – BACKGROUND: Several studies have indicated that semaphorin 5A (SEMA5A) rs7702187 polymorphism is associated with significant increases in risk of Parkinson's disease (PD). However, their results were generally inconsistent and inconclusive.

AIM: The aim of our study was to derive a more precise estimation of the association between the SEMA5A rs7702187 polymorphism and the susceptibility for PD by using meta-analysis.

MATERIALS AND METHODS: We searched and collected articles in English or Chinese from the databases of Medline, PubMed, Embase, and Web of Science (updated to September 31, 2010) by using the search terms "semaphorin gene", "Parkinson's disease", "SNPs" and "polymorphism".

RESULTS: All of these selected studies should meet all of the inclusion criterias such as "case-control studies", "similar study method", "sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI)". As a result, 12 studies in different populations including 3539 cases and 3250 controls were selected.

CONCLUSIONS: Our meta-analysis suggests that the Single-Nucleotide Polymorphism (SNP) of rs7702187 within the SEMA5A gene would be a high-penetrant risk factor for PD development in western population (p = 0.20 for heterogeneity, OR = 0.87, 95% CI = [0.79, 0.96]).

Key Words:
Parkinson's disease, Semaphorin 5A, Single-nucleotide polymorphism, Meta analysis.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases world-wide. The incidence of PD is rising year by year, and onset age has become much younger, which gives rise to great damages to the society as well as the family[1]. Symptoms of PD include muscle rigidity, tremors, and changes in speech and gait[2]. The causes of PD are not clearly known but previous studies have shown that complex environmental and heritable factors may contribute to PD development. In recent years, several genes have been identified as potential PD susceptive genes, such as PARKIN, Leucine Rich Repeat Kinase 2 (LRRK2), and PTEN-Induced Kinase 1 (PINK1)[3-5]. The identification of related genes may help us to investigate the molecular pathological basis of PD, and may contribute to further studying pathogenesis of PD as well as finding out a new therapeutic target.

The gene of semaphorin 5A (SEMASA) is located in 5p15.2, which involves in the process of the neurite growth and cell signal transduction by binding with its receptor plexin-B3[6-8]. Maraganore et al[5], investigated the relationship between SEMA5A gene polymorphism and PD sensitivity for the first time by a Genome Wide Association Study in PD, and the polymorphism SEMA5A rs7702187 was reported to be associated with significant increases in risk of PD[5]. Later, a series of related studies were carried out, however, results were generally inconsistent and inconclusive. Therefore, a meta-analysis was performed here to derive a more precise estimation of the association between the SEMA5A rs7702187 polymorphism and the susceptibility for PD.

Materials and Methods

Publication Search

The publications were searched from the databases of Medline (http://www.nlm.nih.gov/bsd/pmresources.html), PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), and ISI Web of Knowledge (http://isiknowledge.com/). The last search updated on October 11, 2010. The search terms "semaphorin gene", "Parkinson's disease", "SNPs" and "polymorphism" were used. The references of associated publications

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were carefully evaluated to obtain as many as possible. Only those published studies with full-text articles in English or Chinese were included in this meta-analysis. For overlapping and republished studies, only the first one with the largest samples was included.

Inclusion Criteria

The details of our inclusion criteria were as follows: (1) evaluation of the polymorphism of SEMA5A rs7702187 and PD risk; (2) well-designed case–control studies using similar research methods (with strict case selection, international diagnosis standard of PD, and appropriate statistical methods); (3) with sufficient published data to estimate an odds ratio (OR) with 95% confidence interval (CI); (4) written in English or Chinese language; (5) containing detailed and useful genotype frequencies or alleles frequencies. The selected articles should meet all of the above criteria. Studies without clear and full information of samples were excluded.

Data Extraction

Two reviewers extracted information from all eligible publications independently, according to the above inclusion criteria. Due to the conflict, an agreement was signed by discussion between the two reviewers. If these two reviewers could not reach a consensus, another reviewer was consulted to resolve the dispute. We did not define any minimum number of patients for inclusion in our meta-analysis. Then, the following characteristics were respectively collected from each selected study: first author's surname, year of publication, country, ethnicity, menopause status, source of control groups, total number of cases and controls, and numbers of cases and controls with various genotypes.

Statistical Analysis

The risk of PD associated with SEMA5A rs7702187 was estimated for each study[9] by ORs with 95% CI. For all studies, we estimated the association under five different types of ORs, namely the allele contrast model (A vs. T), the homozygote codominant model (TT vs. AA), the heterozygote codominant model (AT vs. AA), the dominant model (TT + AT vs. AA), and the recessive model (TT vs. AT + AA). The level of Hardy-Weinberg equilibrium (HWE) was tested by the method of v2 test. The Q-statistic was used to investigate the degree of heterogeneity between the trials, and a p value of more than 0.10 for the Q-test indicated a lack of heterogeneity among studies. We used the mixed-effects model and the random-effects model to combine values from each of the studies based on the Mantel-Haenszel method and the DerSimonian and Laird Method, respectively[10,11]. If the effects were assumed to be homogenous, the mixed-effects model was then used; otherwise, the random-effects model was more appropriate. The Egger's test and inverted funnel plots were utilized to provide diagnosis of publication bias[9]. A sensitivity analysis was also performed by omitting each study in turn to identify potential outliers. All of the statistical analyses were performed with Review Manager version 4.2 (The Cochrane Collaboration, Copenhagen, Denmark).

Results

The Characteristics of Selected Studies

By searching the databases, 15 abstracts were collected according to the search criteria. Only one publication was about reviews or meta-analyses, and 1 publication was excluded because the study subject was overlapped with another article[12]. Finally, 7 case-control studies involving 2,758 cases and 2,481 controls about the association between SEMA rs7702187 polymorphism and PD susceptibility were included in our meta analysis. Table I and Table II listed main characteristics of these identified studies including 10 studies of western species and 6 studies of eastern species. With consideration of the genetic heterogeneity between western species and eastern species, the subgroup analysis was performed.

Analysis of Genotype Frequencies

When all the studies were pooled, no significant associations were found between the SEMA5A rs7702187 polymorphism and PD susceptibility. In the subgroup analysis by ethnicity, no significant associations between the SEMA5A rs7702187 polymorphism and PD susceptibility were observed (Table III).

Analysis of Allele Frequencies

In the subgroup analysis of eastern population, no significant associations between the SEMA5A rs7702187 polymorphism and PD susceptibility were present. However, the results indicated that an allele named rs7702187 in SEMA5A would

Table I. Genotype frequency distributions of the rs7702187 polymorphic loci in all studies included in the meta-analysis.

Author	Country	Year	PD group (n=2758)				Control group (n=2481)			
			TT	AT	AA	N	TT	AT	AA	N
Ding H[19]	China	2008	220	92	28	340	145	63	14	222
Li Y[17]	UK	2006	215	86	9	310	217	83	8	308
Bialecka M	Poland	2005	172	57	6	235	163	51	6	220
BialeckaM[18]	Singapore	2006	115	68	9	192	116	67	9	192
Clarimon J[16]	Finland	2006	108	32	6	146	93	39	3	135
Clarimon J	Taiwan	2006	129	133	21	303	104	60	7	171
Goris A[22]	UK	2006	356	129	15	500	344	134	13	491
Farrer MJ[20]	Ireland	2006	120	59	2	181	124	46	6	176
Farrer MJ	Norway	2006	216	89	9	314	204	102	12	320
Farrer MJ	USA	2006	172	52	13	237	163	71	12	246

be a high-penetrant risk factor for PD development in western population (A vs. A+T: OR = 0.87, CI = 0.79-0.96).

Sensitivity Analysis and Publication bias

In overall studies, the results suggested that there would be no significant influence of any of the individual data set on the pooled OR values. The Begg's funnel plot and Egger's test similarly failed to reveal evidence of publication bias.

Discussion

Susceptibility to PD is thought to be easily influenced by both genetic and environmental factors and their interactions with each other. On account of difference in race, design, patient selection criteria, and sample size among these studies investigating the relationship between SEMA5A gene polymorphism and PD sensitivity, the results were generally inconsistent and inconclusive.

The gene of SEMA5A belongs to the semaphorin gene family that encodes membrane proteins containing a semaphorin domain and several thrombospondin type-1 repeats. Members of this family are involved in axonal guidance during neural development. This gene has been implicated as an autism susceptibility gene[13]. In most of previous studies, SEMA5A was reported as cancer related. For example, SEMA5A was identified as a novel biomarker for non-small cell lung carcinoma (NSCLC) in nonsmoking women. The down-regulation of SEMA5A in tumor tissue, both at the transcriptional and translational levels, was associated with poor survival among nonsmoking women with NSCLC[14]. Moreover, high gene expression of SEMA5A in pancreatic cancer is associated with tumor growth, invasion, and

Table II. Allele frequency of the rs7702187 polymorphic loci in all studies included in the meta-analysis.

Author	Nation	Year	Quality	PD group (patients)		Control group (control)	
				A	T+A	A	T+A
Ding H[19]	China	2008	5	148	680	91	444
Li Y[17]	US	2006	5	104	620	99	616
Bialecka M	Poaland	2005	5	69	470	63	440
Bialecka M[18]	Singapore	2006	5	86	384	85	384
Clarimon J[16]	Finland	2006	5	44	292	43	270
Clarimon J	Taiwan	2006	5	181	606	75	342
Goris A[22]	UK	2006	5	166	1040	160	998
Farrer MJ[20]	Ireland	2006	5	63	362	58	352
Farrer MJ	Norway	2006	5	107	628	126	640
Farrer MJ	USA	2006	5	78	474	95	492
Maraganore DM[5]	UK	2005	5	121	864	156	864
Maraganore DM	UK	2005	5	87	658	129	658

Table III. Main results of the meta-analysis.

	Western AA genotype	Eastern AA genotype	Western A allele	Eastern A allele	Western T allele	Eastern T allele
Homogeneity test	$p = 0.76$	$p = 0.70$	$p = 0.20$	$p = 0.16$	$p < 0.0001$	$p = 0.16$
OR	OR = 0.99	OR = 1.35	OR = 0.87	OR = 1.05	OR = 1.02	OR = 0.84
95% CI	[0.69, 1.43]	[0.85, 2.14]	[0.79, 0.96]	[0.93, 1.52]	[0.82, 1.27]	[0.70, 1.00]
Z	Z = 0.05	Z = 1.29	Z = 0.36	Z = 1.39	Z = 0.16	Z = 1.93
p	$p = 0.96$	$p = 0.20$	$p = 0.008$	$p = 0.16$	$p = 0.88$	$p = 0.05$

metastasis[15]. SEMA5A was also identified in two genome-wide association studies (GWAS) of PD, such as the study of Maraganore et al[5], or Clarimon et al[16]. It was reported that rs7702187 within SEMA5A was significantly associated with the increasing risk of PD. However, significant associations were not found in other studies, SEMA5A was not implicated in PD risk in a Chinese Han population[17-19]. The results of our meta-analysis suggested that SEMA5A rs7702187 AA polymorphism would be not associated with PD risk, but the SEMA5A rs7702187 allele would be a high-penetrant risk factor for PD development in western population. The large sample size and no significant associations in all genetic models were the two main advantages of this meta-analysis. Heterogeneity was a potential problem that may affect the interpretation of the results. There was no statistically significant heterogeneity in the overall comparisons. No publication biases were detected, indicating that pooled results may be unbiased.

Due to the development of modern biomedicine, many PD related genes were found. Biological functions and roles of these genes in PD were researched[5,17-22]. In recent years, the gene of SEMA5A was found to be related with neurological disease[23]. There are thousands of SNPs in SEMA5A, one of which is Rs7702187 in the intron of SEMA5A with several important regulatory functions. The mutation of intron's splice site may lead to RNA abnormal splice which affects transgenic expression and organism's phenotype[24]. Moreover, a virtual expression database search and RT-PCR analysis showed co-expression of SEMA5A and Plexin B3, and the interaction of SEMA5A with Plexin B3 was confirmed by co-immunoprecipitation studies[25].

Conclusions

Clinical trial and genome-wide association study of gene-disease association, gene-environment interaction, and pharmacogenomic/toxicogenomic revealed that PD is a complex disease. The studies on the structures and functions of related genes will help us to expound the molecular pathogenesis of PD or other neurodegenerative diseases and to find more effective ways of prevention and treatment.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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