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Correlation between CTLA-4 gene rs221775A>G single nucleotide polymorphism and multiple sclerosis susceptibility. A meta-analysis

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Abstract: Objective. The aim of this meta-analysis was to undertake a meta-analysis to evaluate the correlation between cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) gene rs221775 A>G single nucleotide polymorphism and the susceptibility of multiple sclerosis (MS) susceptibility.

Method. Published manuscripts about CTLA-4 gene rs221775A>G single nucleotide polymorphism and multiple sclerosis susceptibility were searched in the computerized bibliographic searches of Pubmed Embase and China National Knowledge Infrastructure (CNKI). Potential studies were screened and data for 5025 MS patients and 4706 controls from 20 publications were included. The association between CTLA-4 gene rs221775A>G single nucleotide polymorphism and multiple sclerosis susceptibility were demonstrated by odds ratio (OR) and 95% confidence interval (95%CI).

Results. The pooled results showed no significant association between CTLA-4 gene rs221775A>G single nucleotide polymorphism and multiple sclerosis susceptibility for dominant genetic model [OR=1.02, 95%CI:0.90～1.05, (P=0.80)], homozygous genetic model [OR=0.85,95%CI:0.71～1.03,(P=0.10)] and recessive genetic model [OR=0.99,95% CI:0.89～1.10,(P=0.90)].

Conclusion. With current evidence, CTLA-4 gene rs221775A>G single nucleotide polymorphism had no association with the susceptibility of multiple sclerosis

Keywords: Multiple sclerosis; CTLA-4 gene; Susceptibility; Polymorphism; Meta-analysis

1 Introduction

Multiple sclerosis (MS) is a kind of demyelinating disease in which the insulating cover of nerve cells in the brain and spinal cord are damaged. And it was reported that MS is the most common diagnosized autoimmune disease which can affect the central nervous system. Clinical epidemology study estimated that about 2,300,000 subjects were affected by MS globally in the year of 2013, and about 20,000 people died from MS at the same year [1]. MS has the ability to reduce the communication of the central nervous system, which can lead to a range of signs and symptoms, including physical, mental, and sometimes psychiatric problems [2]. Generally, MS is not believed to be a hereditary disease, but some studies indicated that the genetic variations could have an association with the increasing risk of developing MS [3]. One of the related genes is cytotoxic T lymphocyte-associated antigen 4(CTLA-4), which is expressed on the surface of T cells and is critical in inhibiting T cell activation. Several studies have reported a significant correlation between CTLA-4 gene rs221775A>G single nucleotide polymorphism and multiple sclerosis susceptibility [4, 5]. However, other studies have not find a significant correlation [6-8]. Thus, we performed a meta-analysis by pooling all the available data related to CTLA-4 gene rs221775A>G single nucleotide polymorphism and multiple sclerosis susceptibility in order to further evaluted the corrlation.

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2 Method

2.1 Publication search strategy

The open published studies about the CTLA-4 gene rs221775A>G single nucleotide polymorphism and multiple sclerosis susceptibility were searched in the databases of Pubmed Embase and China National Knowledge Infrastructure (CNKI). The case-control or cohort studies published in English or Chinese were all searched in the databases before Jan 2016. The search strategy and text words were: "cytotoxic T lymphocyte associated antigen/CTLA-4/CTLA4", "multiple sclerosis/MS" or "polymorphism". The references for the included papers were also screened to identify additional potential suitable studies which were not indexed in the pubmed or CNKI databases.

2.2 Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the study design was cases-cotrol or cohort; (2) the paper was published in English or Chinese; (3) the genotyping method is correct; (4) the frequency of AA, AG and GG nucleotide can be extracted from the original study. And the exclusion criteria were: (1) the study design type were review or case report; (2) studies with duplicate published datas; (3) Studies publised in other languages (not English or Chinese); (4) the data extracted from the original studies was not enough to calculate the ORs.

2.3 Data evaluation

Two reviewers (XIAO Haibing &CAO Xu) of this manuscript independently reviewed the papers and extracted the data according to the Cochrane Handbook. The general information such as first author, the paper publication year, the country of the study performed, and the race of the included subjects for each of the included paper were extacted. The frequency of AA, AG and GG nucleotide for the include 20 studies were canrefully extracted and corss checked, which was used to calculated the pooled ORs. If disagreements were encountered, the discussion was made and a third reviewer was consulted.

2.4 Statistical analysis

Stata/SE 11.0（StataCorp LP, http://www.stata.com）were used for statistical analysis. The correlation between CTLA-4 gene rs221775A>G single nucleotide polymorphism and multiple sclerosis susceptibility was demonstrated by odds ratio (OR) and its 95% confidence interval (95%CI). Statistical heterogeneity among studies was evaluated by I^2 [9]. If significant heterogeneity was found (I^2＞50%), the random-effect method (Dersimonian-Laird method) was used to pool the data. Inversely, fixed-effect method was applied.

The publication bias was detected by Begg's funnel plot.

3 Results

3.1 General information of the included studies

Through searching the databases, 86 related publication were initial identified. 66 studies were excluded after reviewing the complete text. Overall, we included twenty published articles in this meta-analysis with 5025 MS patients and 4706 controls. For the inlcuded 20 open published studies, 14 articles included the subjects with race of Caucasus, 3 with Arab, 1 with mixed, 1 with Asian and 1 with Australoid. The publication year ranged form 1999 to 2011. All papers were published in English. General information of the included 20 papers are demonstrated in Table 1 .

3.2 Dominant genetic model (GG+AG vs AA)

For the dominant genetic model (GG+AG vs AA), significant heterogeneity across the included twenty article existed (I^2=82.5%, P=0.00). The OR was pooled by random effect model. The pooled OR was 1.06 and 95% confidence interval was 0.86～1.30 wich indicated that there was no significant association between CTLA-4 gene rs221775 A>G single nucleotide polymorphism and multiple sclerosis susceptibility in dominant genetic model (GG+AG vs AA (Figure 1). The begg's funnel plot indicated no significant publication bias (Figure 2).

Table 1. General information for the included studies

Authors	Year	Country	Race	No		Case			Control		
				MS	Control	AA	AG	GG	AA	AG	GG
Ligers etal[4]	1999	Sweden	Caucasus	378	237	117	188	73	83	123	31
Rasmussen(1) et al[6]	2001	Denmark	Caucasus	84	125	28	39	17	35	68	22
Rasmussen(2) et al[6]	2001	Denmark	Caucasus	42	86	4	23	15	7	34	45
Andreevskii et al[7]	2002	Russia	Caucasus	168	209	51	85	32	68	104	37
Masterman et al[8]	2002	Sweden	Caucasus	374	290	120	188	66	82	139	69
Maurer et al[5]	2002	Germany	Caucasus	330	152	132	157	41	66	69	17
Bocko et al[10]	2003	Poland	Caucasus	102	101	31	57	14	35	53	13
Kantarci et al[11]	2003	USA	Mixed	120	235	45	59	15	89	111	35
van Veen et al[12]	2003	Netherlands	Caucasus	514	181	215	229	70	72	85	24
Bilinska et al[13]	2004	Poland	Caucasus	152	154	47	80	25	50	84	20
Teutsch et al[14]	2004	Australia	Caucasus	102	152	30	54	18	64	61	27
Fukazawa et al[15]	2005	Japan	Asian	133	156	23	69	41	29	66	61
Lorentzen et al[16]	2005	Norway	Caucasus	513	509	164	251	98	168	249	92
Malferrari etal [17]	2005	Italy	Caucasus	95	104	40	46	9	37	54	13
Dincic et al[18]	2006	Montenegro	Caucasus	162	102	96	56	10	41	52	9
Heggarty et eal[19]	2007	England	Caucasus	330	158	129	148	53	46	84	28
Greve(1) etal [20]	2008	Poland	Caucasus	180	171	59	96	25	49	90	32
Greve(2) etal[20]	2008	Germany	Caucasus	200	464	75	90	35	178	216	70
Greve(3) etal[20]	2008	Hungary	Caucasus	193	91	64	96	33	32	48	11
Wray et al[21]	2008	Australia	Australoid	198	224	65	111	22	86	107	31
Yousefipour et al [1]	2009	Iran	Arab	153	190	79	56	18	117	59	14
Heidari et al[22]	2010	Iran	Arab	135	135	42	69	24	38	74	23
Cizmarevic et al[23]	2011	Iran	Arab	367	480	151	165	51	198	221	61

3.3 Homozygous genetic model (GG vs AA)

For the homozygous genetic model (GG vs AA), no significant heterogeneity across the included 20 articles were found (I^2=0.80%, P=0.45). So, the OR was pooled by fixed effect model. The pooled OR showed no significant correlation between CTLA-4 gene rs221775 A>G single nucleotide polymorphism and multiple sclerosis susceptibility was found in homozygous genetic model (GG vs AA) (Figure 3). The pulication bias was evaluated by funnel plot, which indicated no significant publication bias (Figure 4).

3.4 Recessive genetic model (GG vs AG+AA)

For the recessive genetic model (GG vs AG+AA), the heterogeneity across the studies were assesed by I^2 which showed no significant heterogeneity across the studies (I^{2s}=81.2%, P=0.45). We pooled the data by fixed effect mode. The pooled the results indicated no statistical association between CTLA-4 gene rs221775 A>G single nucleotide polymorphism and multiple sclerosis susceptibility in recessive genetic model (GG vs AG+AA) (Figure 5). And begg's funnel plot was symmetric which indicated no significant publication bias (Figure 6).

4 Discussion

Generally, the causes for MS is unclear. However, it is believed that it could be the result of a combination of genetic and environmental factorial influences (such as infectious agents) [24]. Results of publised studies have demonstrated that some genetic variations can increase the risk of developing MS [11]. These genes seem to be

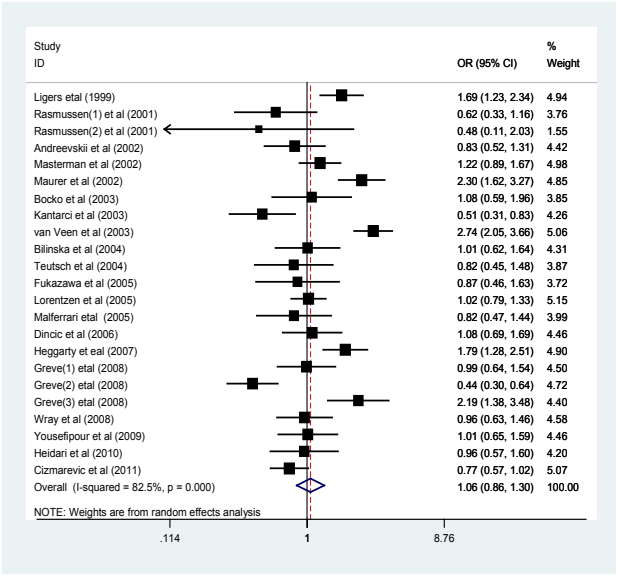

Figure 1: The forest plot of OR for CTLA-4 gene rs221775 A>G single nucleotide polymorphism and multiple sclerosis susceptibility under dominant model (GG+AG vs AA).

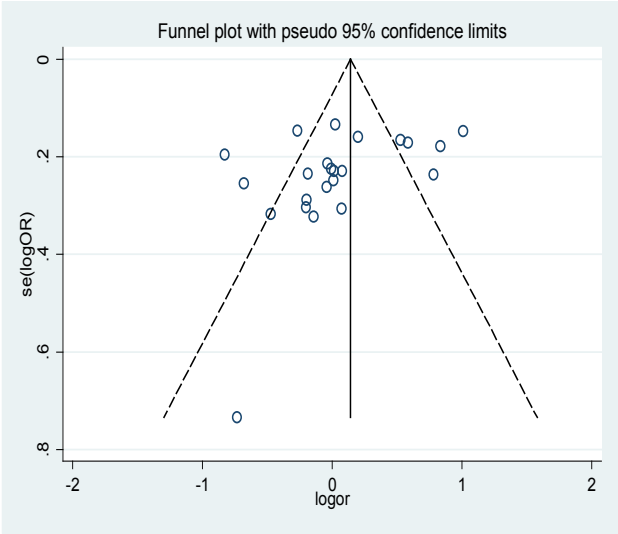

Figure 2: The Begg's funnel plots showe no significant publication bias under dominant model (GG+AG vs AA)..

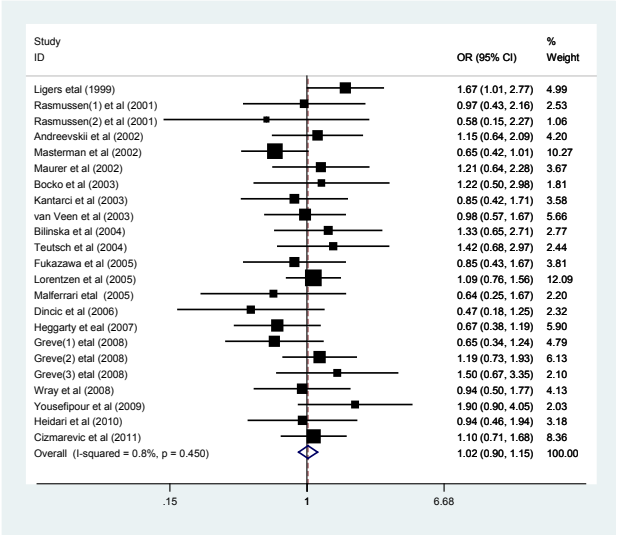

Figure 3: The forest plot of OR for CTLA-4 gene rs221775 A>G single nucleotide polymorphism and multiple sclerosis susceptibility under homozygous genetic model (GG vs AA).

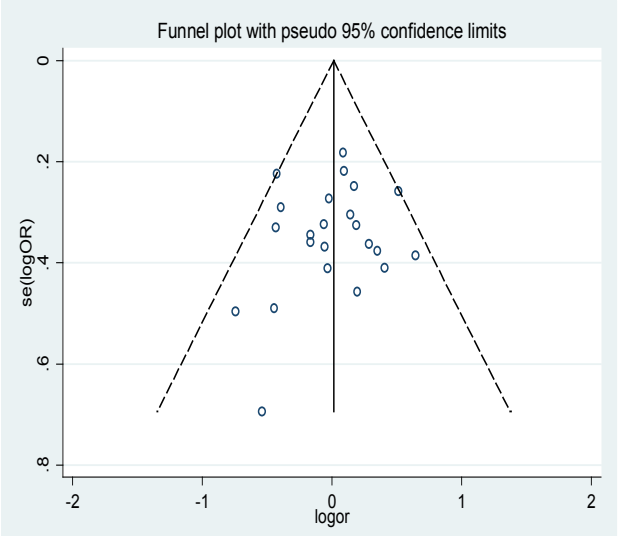

Figure 4: The Begg's funnel plots showe no significant publication bias homozygous genetic model (GG vs AA).

expresed higher in microglial cells than expected by chance. Cytotoxic T-lymphocyte-associated protein 4 gene was one of these genes that was positive expressed in activated T lymph cells and played an important role in inhibiting the function of T lymph cell [25].

CTLA-4, also known as CD152 (cluster of differentiation 152), is a protein receptor that functions as an immune checkpoint, downregulates the immune system. Animal experiment showed that disruption of CTLA-4 leads to fatal lymphoproliferative disorder, which could result in a widespread autoimmunity in mice [26]. Recently, seveal studies have found the cytotoxic T-lymphocyte-associated protein 4(CTLA-4) gene rs221775A>G single nucleotide polymorphism to be associated with the susceptibility of multiple sclerosis [4, 19]. Heggarty and his colleges [19] discussed the relationship between CTLA4 gene polymorphisms and multiple sclerosis risk in Northern Ireland. They found that people with A allele and AA genotype of rs221775 had more risk of developing MS (OR=1.36, P<0.05 for A allele and OR=1.81, P<0.05 for AA genotype).

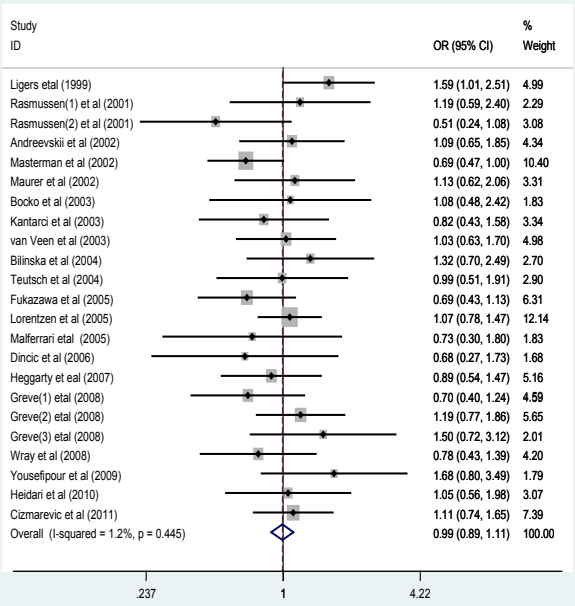

Figure 5: The forest plot of OR for CTLA-4 gene rs221775 A>G single nucleotide polymorphism and multiple sclerosis susceptibility under recessive genetic model (GG vs AG+AA)

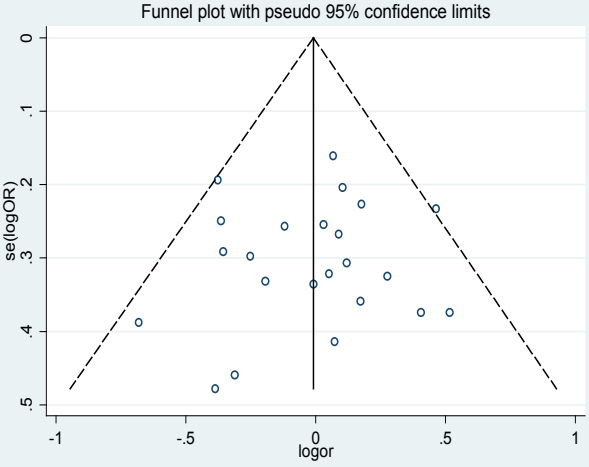

Figure 6: The Begg's funnel plots showe no significant publication bias under recessive genetic model(GG vs AG+AA)

Significnat correlation between CTLA-4 gene rs221775A>G single nucleotide polymorphism and MS risk was demonstrated in their study. Kantarci et al [11] also found that CTLA4 was associated with susceptibility to multiple sclerosis. They performed a population-based sample of 122 sporadic patients with MS and 244 age-, gender- and ethnicity-matched controls, and by linkage and family-based association methods in 395 individuals from 59 American multiplex pedigrees with 141 affected individuals. They found a strong association with age at onset, disease course and severity. Moreover they found that CTLA-4 was associated with the susceptibility to MS.

On the other hand, Greve et al [20] found no association between CTLA4 polymorphism and MS susceptibility in patients from Germany, Hungary and Poland. Thus, the results for CTLA4 polymorphism and MS risk is not conclusive within published articles. The current meta-analysis pooling of publised data were preformed in order to further evaluated the correlation between CTLA4 gene polymorphisms and multiple sclerosis. We included 20 studies involving 5025 MS patients and 4706 controls. No significant correlation between CTLA4 polymorphism and MS in dominant genetic model (GG+AG vs AA), homozygous genetic model (GG vs AA) or recessive genetic model(GG vs AG+AA) genetic model were found.

There are several limitations with the present meta-analysis to be considered. Firstly, heterogeneity existed in dominant genetic model (GG+AG vs AA), which could reduce the statistical power for pooling the data. Secondly, only paper published in English or Chinese had been screened in the databases and include. Thirdly, MS is a complex diseases, which is the result of the combined actions of multiple susceptibility genes and one or more environmental factors, and only the association between one single nucleotide polymorphism for one gene was evaluated which may not be enough.

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Conflict of interest statement: Authors state no conflict of interest.

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